THE

REPORT

OF THE

DEPARTMENT OF PATHOLOGY

OF

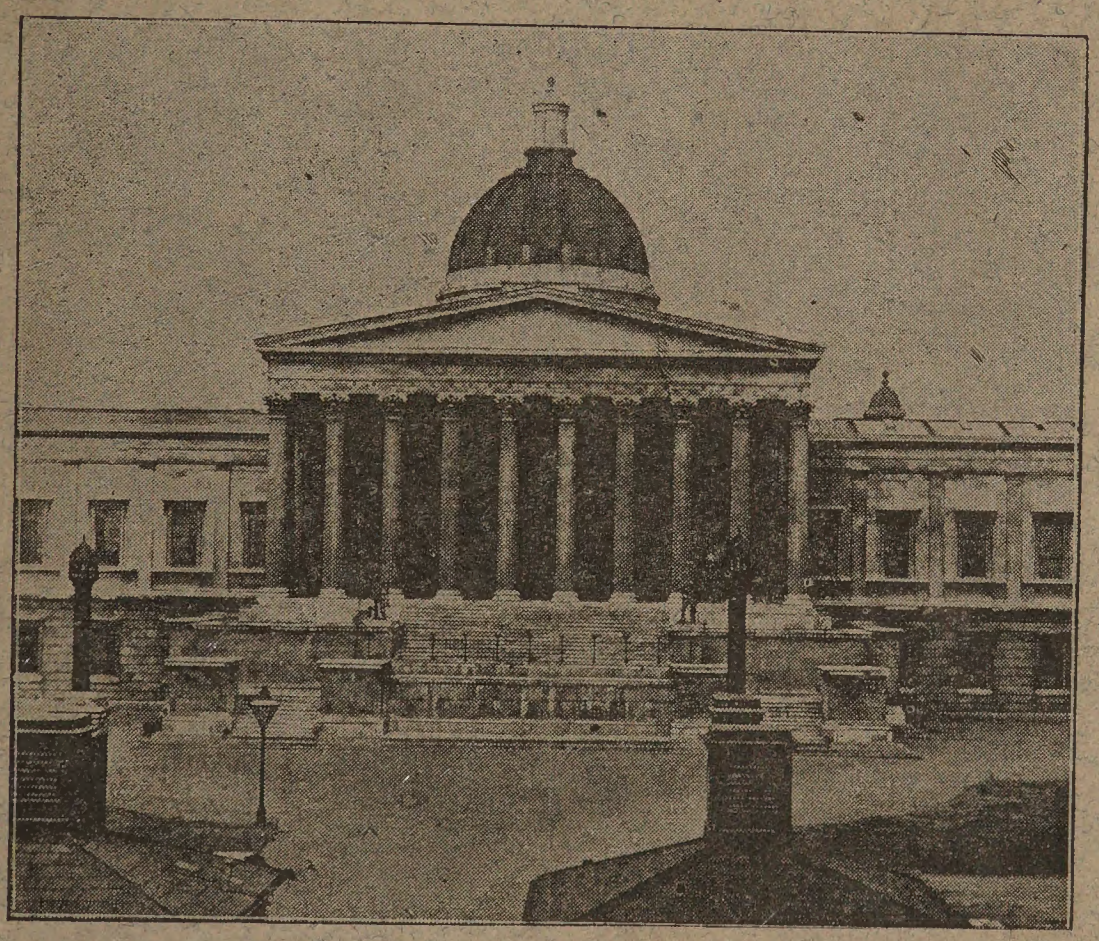
UNIVERSITY COLLEGE, LONDON.

December, 1893.

TOGETHER WITH A

COLLECTION OF PAPERS AND ABSTRACTS PUBLISHED FROM THE LABORATORY.

VOL. II.



EDITED BY

VICTOR HORSLEY, F.R.S., F.R.C.S.

PROFESSOR OF PATHOLOGY, UNIVERSITY COLLEGE;

RUBERT BOYCE, M.B.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY COLLEGE;

AND

VAUGHAN HARLEY, M.D., M.R.C.P.,

TEACHER OF CHEMICAL PATHOLOGY, UNIVERSITY COLLEGE.

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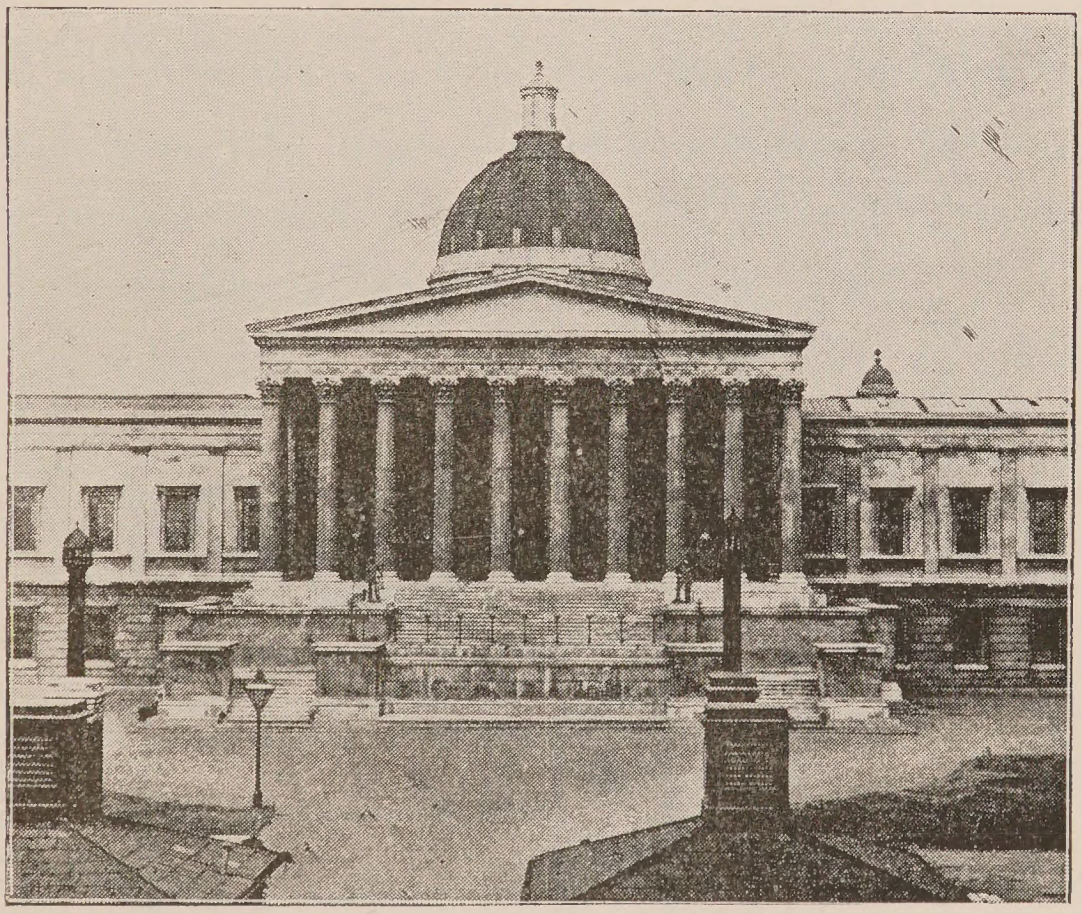

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INTRODUCTION.

The present volume forms the second which has appeared from the laboratory this year. Since the publication of the first volume in August, it has been thought more desirable to issue the reprints thrice yearly or even more often; the size of each volume may be thus sacrificed, but the material is more recent.

The advisability has also been considered of including reprints of papers published by Students of the Laboratory, bearing upon subjects of experimental interest; to this category belongs the paper of Dr. Beadles on Myxœdema and Cretinism.*

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* Owing to the difficulty of binding, the papers in the Philosophical transactions do not appear in this collection. They include—

The minute analysis of the facial region of the so-called facial region of the Macacus rhesus, by VICTOR HORSLEY, F.R.S., F.R.C.S., and CHARLES BEEVOR, M.D., M.R.C.P.

The nerve roots which enter into the formation of the brachial plexus, etc., of the dog, by RISIEN RUSSELL, M.B., M.R.C.P.

INDEX.

NEUROLOGY.

W. LLOYD ANDRIEZEN, M.B.—The Neuroglia Elements in the Human Brain. From Brit. Med. Journal, July, 1893.

RUBERT BOYCE, M.B.—Changes following removal of one Cerebral Hemisphere. Abstract in Brit. Med. Journal, November, 1893.

RISIEN RUSSELL, M.D., M.R.C.P.—An Experimental Investigation of the Nerve Roots, which enter into the formation of the Lumbo—Sacral Plexus of Macacus Rhesus. From. Proc. Roy. Soc., Vol. 54, 1893.

On some circumstances under which the normal state of the Knee Jerks is altered. From Proc. Roy. Soc., Vol. 53, 1893.

CHEMICAL PATHOLOGY AND METABOLISM.

VAUGHAN HARLEY, M.D., M.R.C.P.—Diabetic Coma; its Etiology and Suggestions as to Treatment. From Brit. Med. Journal, Sept , 1893.

Influence of Sugar in the circulation on the Respiratory Gases and Animal Heat. From Journal of Physiology, Vol. 15, 1893.

CECIL F. BEADLES, M.R.C.S., L.R.C.P.—The Treatment of Myxœdema and Cretinism. From Journal of Mental Science, July and October, 1893.

BACTERIOLOGY.

S. P. KRAMER, M.D. and RUBERT BOYCE, M.B.—The Nature of Vaccine Immunity. From Brit. Med. Journal, Oct., 1893.

J. E. BOCARRO, L.M. & S., Bombay.—An Analysis of One Hundred Cases of Mycetoma (Madura disease). From Lancet, Sept., 1893.

MAX WALTHARD, M.D., (Bern.), and M.R.C.S., (Eng.).—On the Etiology and Prevention of Peritoniel Adhesions. Translated from the Correspondenz-Blatt, Schweiz. Aerzte, Jahrg. XXIII., 1893.

Reprinted for the Author from the BRITISH MEDICAL JOURNAL,
July 29th, 1893.

THE NEUROGLIA ELEMENTS IN THE HUMAN BRAIN.

BY W. LLOYD ANDRIEZEN, M.B.LOND.,
From the Pathological Laboratories of University College, London, and the West Riding Asylum, Wakefield.

THE present preliminary account deals only with the neuroglia elements in the human brain. The research was begun at University College in May, 1892, and continued at the laboratory of the West Riding Asylum since January last. The whole material examined consists of twenty-seven human brains, and the regions studied were the ascending frontal, the occipital (or calcarine), and the hippocampal regions of the brain.

Among animals studied were fœtal, young and adult cats, adult rats, rabbits, cats, and the ox; the results obtained from these confirm in the main features those obtained in the human brain. While in the human brain the nerve elements have been largely and extensively studied both in health and in disease, the neuroglia elements have been comparatively neglected, partly owing to a widely-spread belief in a mere passive *rôle* they were supposed to play, and partly owing to inadequacy of the methods used, for while the general and special methods with the anilines, picro-carmine, osmic acid, hæmatoxylin, and gold chloride—to mention only the chief—have shown much of the nerve elements, a method has been wanting which should not only exhibit the former elements down to their finest ramifications and actual endings, but should do the same for the neuroglia elements with faithfulness and precision, so as also to demonstrate the relations of these two elements to another and to the ground substance.

This is now possible by Golgi's method of staining with silver chromate, which since 1886 marked an epoch in neurology, of which the publication of his great work *Sulla fina Anatomia dela Sistema Nervosa* was the beginning of a revolution of our old ideas on the mechanism and mode of action of the nervous system which is still in progress. With young and embryonic nervous systems that method gives the best results; with slight modifications it has given in my hands results of much success for the adult brains of animals, and by a rather more modified process, similar, and in some respects better, results have been obtained for the human brain. The results obtained in the present research were due to such a method, the details of which will be published later.

From each of the specimens of human brain used, forty to sixty sections were selected and mounted for study: thus, on

the whole, rather more than a thousand sections were used, while, of these, only those on which the staining was most precise, uniform, and perfect were utilised to elucidate the details of the neuroglia elements as below. Such an investigation soon made it evident that the neuroglia elements present possess such marked differential characters among themselves that they obviously form two great morphological groups, which, from their most striking appearance, may be justly called (*a*) the neuroglia fibre cell, (*b*) the protoplasmic neuroglia cell. The classification here proposed, and, as far as I am aware, for the first time, while *primâ facie* morphological, is also, as will be shown, a physiological one, while

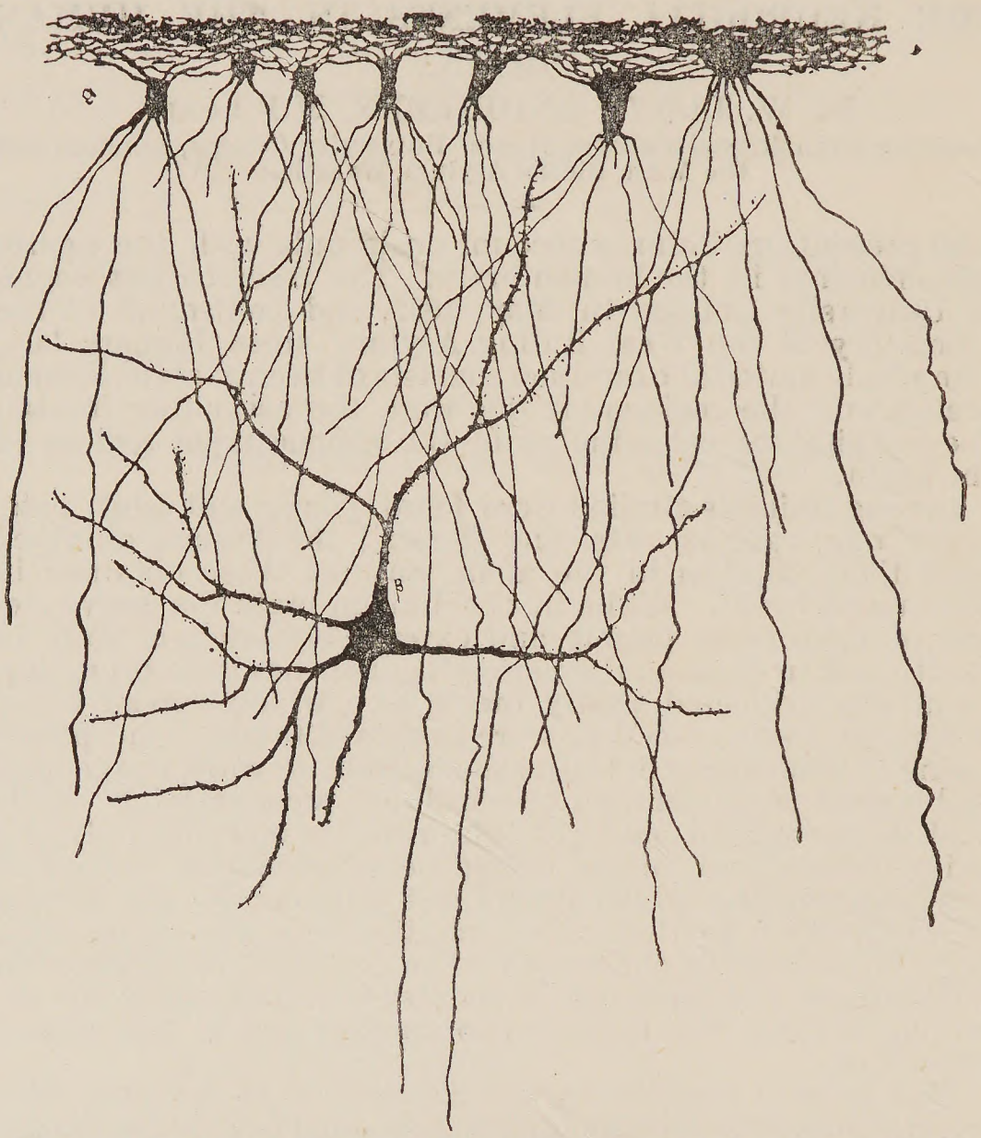

Fig. 1.—*a*. Seven caudate neuroglia fibre cells of the first layer of the human cortex, sending processes some of which reach one-half way down the depth of the cortex nearly to the midst of the third layer. *β*. One small pyramidal nerve cell of the third layer (upper part of).

independent studies on their etiology and pathology all point in the same direction, as will be evident shortly. The illustrations accompanying were drawn by the aid of Schroeder's camera lucida.

A. The Neuroglia Fibre Cell.

There are two species of this cell (see Figs. 1 and 2), and their topographical distribution is corresponpingly different. One species (*α*) is situated in the first layer of the cortex, and

sends its streaming fibres down into the third layer; these are the caudate cells (Fig. 1). The other (β) is situated in the medullary substance or white matter, and has radiating fibres passing in all directions (stellate fibre cells, Fig. 2).

1. *The Caudate Fibre Cells.*—These form a distinct feature in the first layer of the grey matter in specimens of human brain. The cell bodies are imbedded in the grey substance,

Fig. 2.—Two neuroglia fibre cells of the medullary substance or white matter of the human brain (Schroeder's camera lucida drawings).

and are the most superficial in position of cell elements—whether nerve or glia—in the cortex. The cell bodies have a rounded apex pointing downwards, and giving rise to a tail-like tuft of smooth fibres streaming into the deeper layers of the cortex. The wider and flatter base is directed towards the surface, and gives origin to an entirely different system of

radiating tangenital fibres. (Fig. 1.) The individual fibres are extremely long, smooth contoured, and of uniform calibre throughout, of remarkably uniform thickness one with another, unbranched, slightly wavy in their course, which is, on the whole, almost rectilinear, and exhibiting here and there small sharp curves and small angular beds, while sharp transverse fractures are not infrequent. They form a fine fretwork of cortical fibres. The caudate cells thus have two if not three systems of fibres : (1) the descending apical (tuft of) fibres which pass deeply into the grey matter ; (2) the superficial tangenital system of fibres forming a true felt-work ; and (3) a few shorter fibres passing to the superjacent pia. None of the fibres anastomose, and none show any special vascular connections.

The Stellate Fibre Cell.—This has been recognised by most observers, especially in the white matter and septa of the cord, and can be isolated by maceration in 30 per cent. alcohol (Ranvier). This form of stellate cell, however, is entirely distinct—as shall be shown—from, and should not be confounded with, the protoplasmic glia cells, which also have a stellate shape in general, and which with the ordinary methods show but little apparent difference from the stellate fibre cell. The distinction here too clearly comes out when these are studied by Golgi's method. Hitherto all neuroglia cells in the adult brains have been included under one category of "spider" cells (Deiters, Meynert, and others), which others have named stellate cells. But it can be demonstrated that these form two distinct, and in many respects opposed, groups—namely, into stellate fibre cells and stellate protoplasmic cells showing important and fundamental differences. In the stellate fibre cell a distinct cell body is hard to recognise, partly owing to the enormous number of fibres which emerge from and intercross in the cell body, and so obscure and conceal it, partly owing to optical diffraction effects at the body or focus where so many fibres meet and decussate, and partly because there is but a small and scanty remnant of protoplasm to constitute the cell body. With a wide angle of light perfectly focussed and free from chromatic aberration, and with equally good lenses, the best preparations will show only a very small quantity of protoplasm in the cell body, which, however, is mainly constituted of the meeting and intercrossing fibres. (Fig. 2.) Many of these neuroglia fibres therefore pass right through the cell body. In calibre and contour they are remarkably like the fibres of their congeners the caudate fibre cells, and exhibit the same peculiar sharp curves and angular bends in a course otherwise straight, and also the same sharp transverse fractures. They stain, too, of the same colour, never branch or anastomose, are of considerable length (being on an average five to eight times as long as the processes of the protoplasmic neuroglia cells), and do not exhibit the special vascular attachments which the protoplasmic glia cell exhibits. It should therefore be distinguished from the next great class of neuroglia elements—namely, the protoplasmic glia cell.

B. The Protoplasmic Glia Cell.

This occurs abundantly throughout the grey matter in all the layers of the cortex, while the stellate fibre cell is absent from, or only most sparingly present in, the grey cortex; while,

on the other hand, it is exceedingly abundant in the medullary substance, where the protoplasmic glia cell is correspondingly rare.

The protoplasmic glia cell has a distinct cell body, which is irregularly oval, frequently pyriform. Its processes are but of slight or moderate length relatively to the fibres of the neuroglia fibre cell, which are from five to eight times as long. The appearance of the protoplasmic glia cell is highly characteristic, and in specimens stained with silver chromate it is impossible to confound these cells (Fig. 3), with the neuroglia fibre cells (Fig. 2). The various protoplasmic processes also exhibit great variations of calibre, some being stout and coarse, and others exceedingly fine (see Fig. 3). The protoplasmic processes are also denditric, a thing never seen in the stellate fibre cells. A most striking feature is the shaggy granular contour, as if a fine moss constituted the protoplasmic processes. The neuroglia fibres

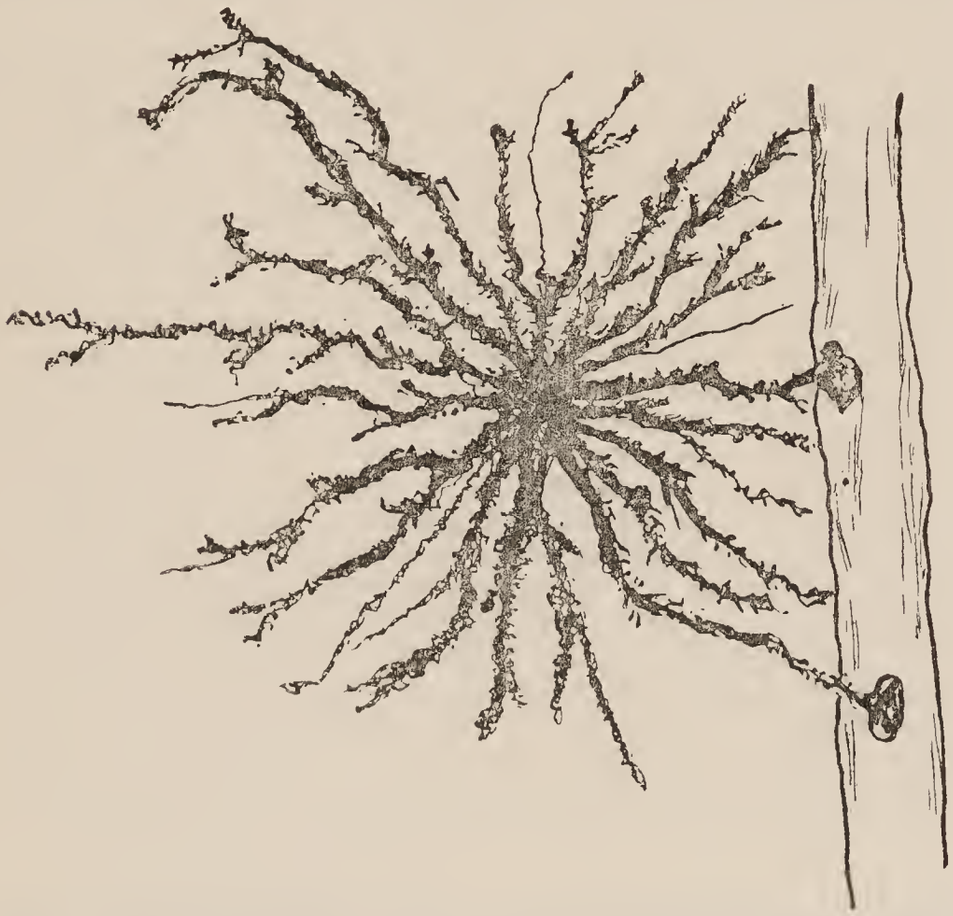

Fig. 3.—A protoplasmic neuroglia cell from the human brain (fourth layer of cortex), showing two expanded conical disc-like attachments to a vessel. Highly magnified.

with good illumination have a deep brown, which is slightly translucent, giving these fibres almost a horny appearance; the dendritic shaggy granular protoplasmic processes, on the other hand, take a distinct reddish-grey tint. Further, by one or more of their coarser processes, the protoplasmic cells are attached to the perivascular sheaths (Fig. 3). The cells of the perivascular sheath can be seen in fortunate preparation to give forth processes which stream into the circumjacent brain substance, and are granular, and resembling the finer protoplasmic processes above described in appearance and coloration. Finally, a fact of the utmost significance, and one clearly demonstrated by the silver staining,

is the presence of a lymph space surrounding the protoplasmic glia cells and its branches, and directly continuous with the perivascular lymh spaces, for it not infrequently happens—unless precautions are taken to prevent it—that, in addition to the intimate staining of the nerve and glia elements, a fine dark precipitate of silver chromate takes place in the perivascular spaces and on the surface of the cortex. In the very regions where this occurs, the protoplasmic glia cells, which, when their intimate structure is stained, present the normal appearance as in Fig. 3, may show the superadded surface deposit, and this deposit is continuous over the vascular processes, and so with that in the perivascular spaces. Sometimes the deposit will not have gone on to cover all the processes, so that those which stand out naked and uncovered exhibit the usual appearances as in Fig. 3. These appearances—which can be repeatedly verified—seem to demonstrate not only the well-known perivascular lymph space, but also a system of lymph spaces surrounding the body and dendritic processes of the protoplasmic glia cells, and directly continuous with the perivascular lymph space. The neuroglia fibre cells exhibit no such lymph spaces. Thus it is clear that the neuroglia elements of the brain are not a uniform structure, nor can their functions be regarded as correspondingly simple and uniform. For the fibre cell elements and the protoplasmic cell elements stand opposed to each other; the former constituting a plexus system of well organised fibres which form a passive supporting feltwork in the brain, while the latter constitute a group of active protoplasmic elements present in abundance only in the grey matter, and having vascular and lymphatic relations of a striking character, and one which points to their active *rôle* in the circulatory and lymphatic economy of the brain.

Finally it can be shown that the protoplasmic glia cells with vascular attachments are mesoblastic in origin; and that the fibre cells (both caudate and stellate) are epiblastic in origin. Thus in the olfactory epithelium we have a differentiation of the primitive epiblast into sustentacular cells and bipolar nerve cells—situated between the basement membrane and the surface. No vessels or other connective elements have ingrown. In the more complex retina—which also is free from connective or other mesoblastic elements—the epiblast has given rise to three superposed layers of nerve elements, and to a well marked system of sustentacular elements, the fibres of Müller. In the embryonic spinal cord the primitive epiblast shows an early differentiation into nerve elements and supporting elements (neuroblasts and spongioblasts of His) and the distinction is obvious and can be recognised before the invasion of mesoblastic elements (blood vessels and connective tissue) from the outside.[1] In the embryonic cord of the chick and of amphibia similar observations have been announced.[2] In all these we have sustentacular elements of epiblastic origin, contemporaneous in origin with the nerve elements, and continuing into adult life as sustentacular structures (fibre cells). The protoplasmic glia cells—those connected with vessels—are to be regarded as ontogenetically younger, and derived from connective elements which have come in with the ingrowth and invasion of vessels, and developed in large numbers in the

[1] His, *Archiv f. Anat. u. Phy.*, 1889. Golgi, *Sulla fina Anatomia*, 1886.
[2] Cajal, *Estructura de la Medula Espinal de los Reptiles*, 1891.

cerebral cortex. The fibre cells, judging from their numbers in the adult brain—especially the cortex—would seem to have produced an enormous number of wavy fibres of great length, while in the very act of such extraordinary fibrillation there protoplasm is used up and exhausted, only a small remnant persisting to mark the cell body. Finally, as instructive analogies may be pointed out the epithelial cells of the Malpighian layer of the epidermis which presents fibrils passing through the cell bodies and constituting the intercellular "bridges" (Ranvier), comparable to the fibres passing through the cell bodies in the stellate neuroglia fibre cells; for were the epithelial cell bodies further apart, and the fibrils relatively longer, their appearance would be not unlike that of the stellate neuroglia fibre cells, an analogy which strengthens the relationship (by genesis) of the neuroglia fibre cells to epithelial elements.

The protoplasmic glia elements are really the elements which exhibit a morbid hypertrophy in pathological conditions (alcoholism, G.P.), and which may show further morbid activities, in the last stage of which their protoplasm will deposit numerous organised fibrillæ, in the act of doing which the protoplasm proper is used up, except a scanty remnant, which may persist, ghost-like, to mark the position of what was once a protoplasmic cell body.

Thus in fundamental facts of structure, in their topographical distribution, in ontogenesis, in their relationships to vascular and lymphatic systems, and in the morbid changes they show it would seem that there are ample grounds for supporting the classification of the neuroglia elements into protoplasmic cells and fibre cells. The growing importance of these elements is becoming daily obvious, especially in brain pathology.

The above results, together with other details on the structure and mechanism of the neuroglia fibre systems, which exhibit not only the surface fretwork of fibres (as in Fig. 1 *sup.*), but also a complex and condensed feltwork of cells and fibres surrounding the blood vessels of the brain,[3] justify the proposal of the following scheme of classification which is here for the first time put forward by the author as a contribution towards a more correct understanding of the neuroglia elements of the brain:

I. *The unorganised homogeneous neuroglia ground substance.*

II. *The organised neuroglia elements.* These latter fall into

α. Protoplasmic elements.

β. Fibre elements.

α. *Protoplasmic Elements* (plasmatic cells) of mesoblastic origin.

(1) *Vascular* (attached to). See Fig. 3 *supra.*

(2) *Pericellular* (surrounding the larger nerve cells as they lie in their pericellular sacs).

β. *Fibre Elements* (fibre cells, sustentacular cells), which in shape may be *caudate*, *stellate*, or *elongate*. These form

(1) A condensed surface feltwork (surface condensation system, Fig. 1).

(2) A somewhat similar perivascular condensation system.[3]

(3) A diffuse network of fibre elements (Fig. 2) pervading all the rest of the brain substance (diffuse system).

[3] A full account of its histology and functional significance is in the author's article in *Intern. Monat. f. Anat. u. Physiol.*, 1893.

Reprinted from the British Medical Journal, November, 1893.

CHANGES FOLLOWING REMOVAL OF ONE CEREBRAL HEMISPHERE.

[*Preliminary Report.*]

By Rubert Boyce, M.B.,

Assistant-Professor of Pathology, University College, London.

Observations have been made upon thirty-five cats, which recovered from the operation and which lived from three days to two-and-a-half months. Parts removed: The hemisphere is divided through the corpus callosum and the crus flush with the tentorium, the knife passing obliquely through the posterior corpora quadrigemina, the grey nuclei are removed as completely as possible. Symptoms: Under most favourable circumstances the animal may walk around its cage in two hours after operation; it shows, however, a perceptible weakness on the right side. In other cases progression on the four limbs takes place in from twelve to twenty-four hours. If there is pressure, however, recovery is much longer. The following are the usual symptoms: The animals are slightly awkward upon the corresponding side of the lesion (left hemisphere always removed), they ascend stairs with left foot first and jump heavily. They can climb, mew, and purr. They always turn to the left (one exception in 35 cases), due to the fact that they are completely blind and probably completely deaf upon the right side. The sense of smell is very greatly reduced. The field of vision of the left eye appears diminished. Pupil reflex in right eye almost completely absent. When the left eye is shaded the right eye dilates in spite of a beam of light. Many complex acts are performed, such as washing the face on the right side. Sensation remains very considerably less on the right side. Not much alteration of the knee-jerks, if anything the reflex is more clonic upon the right side but not so powerful as upon the left side. The animals feed themselves with difficulty owing to

diminution in the senses of smell and sight and probably of taste. The actual amount of paresis is therefore very slight, there is some awkwardness of gait, and there is very distinct diminution of sensation. Compared with cats with hemisection of the cord, the paralysis and loss of sensation is much less profound. Compared with cats in which one lobe of the cerebellum is removed the incoordination in these is more marked, but the amount of paresis in the hemisphere cats is greater for the same date; thus there is not wrist-drop in the cerebellum cats; there is likewise diminution of sensation in the cerebellum cats. It is important to bear in mind these phenomena when studying the effects of absinthe excitation. Paths of degeneration: These have been investigated in 32 cats and the results have been remarkably constant. The Marchi method of staining has been exclusively employed. The results are as follows: Distinct signs of degeneration may be observed as early as the fifth day in the crusta and upper portion of the medulla. Earlier than this date the Marchi method gives no reaction, thus showing that the staining is not accidental. Definite tracts degenerate, there is no irregular staining reaction. The degeneration is well marked between the tenth to fourteenth day, but the Marchi method gives a reaction two months and a half after operation. The total amount of degeneration is very slight, and this corresponds with the very slight and transitory paralysis. In the remaining hemisphere degeneration spreads across the corpus callosum, and tends to turn upwards, but it does not appear to spread far. Degeneration is observed in the commisural fibres in the pineal body. In the crus, pons, medulla, and cord the pyramid of the side of the lesion degenerates and extends to the lumbar region, but it greatly decreases in extent as it descends. There is no trace of degeneration in the opposite pyramid in the crus, pons, or medulla. The degenerate pyramid shows a marked tendency to atrophy, and its connective tissue stains more deeply than that of the sound side. Crossing from the seat of lesion (at the level of the post., corpora quad., and third nerves), degenerate fibres pass over to the opposite side and descend in about the position of the fillet, and are continued down the cord, lying close to and partly intermingled with the fibres of

the pyramid after they have decussated ; they extend equally far with the pyramid. Portion of the fibres which cross, however, turn down close to the raphe, and proceed down the cord as far as the upper dorsal region, lying forwards and close to the middle line in the anterior column (position of so-called direct pyramidal tract). A distinct bundle of fibres starts from about the level of the third nerve on the side of the lesion, and in the position of the posterior longitudinal bundle, and descends to as far as the upper dorsal region; in the cord it occupies the hinder and inner part of the anterior column. Thus in the anterior column on the opposite side of the lesion the degenerate fibres occupy a more anterior position, whilst on the side of the lesion a more posterior position. This relationship is preserved throughout. On the same side of the lesion, and when apparently the latter penetrates far into the mesencephalon, fibres descend on the same side in the position of the fibres in the fillet, mentioned above, upon the opposite side. These lateral fibres on the side of the lesion may extend far down in the cord, and the appearance of two degenerate pyramidal tracts is closely simulated. A bundle of fibres descends in the position of the descending root of the fifth nerve, and passes out by the sixth and seventh nerves ; they are on the side of the lesion. Degenerate fibres have been seen in both third nerves. There is no direct pyramidal tract in the cat.

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THE SEAT OF ORIGIN AND PATHS OF CONDUCTION OF THE FITS IN ABSINTHE EPILEPSY.

[*Preliminary Report.*]

By Rubert Boyce, M.B.,

Assistant Professor of Pathology, University College, London.

The Action of Absinthe.

The action of this drug has been investigated by Marie, Magnan, and Professors Horsley and Gotch ; and these observers have shown the striking resemblance between the fits produced by Absinthe and those seen in idiopathic epilepsy. In the Absinthe fit there

are twitchings of the muscles of the face and ears, which are immediately followed by clonic and tonic spasms of the limb and trunk muscles; there is salivation, the urine is often passed, cries are frequent, and finally a state of unconsciousness may supervene; there is a succession of fits. These toxic effects sufficiently resemble those seen in epilepsy to suggest a toxic origin in some cases of the latter, and to indicate the value of absinthe in the study of the seat of origin of the epileptic fit.

Methods of Procedure.

To try and arrive at the part played by the various divisions of the central nervous system in the production of the fit, the following methods of analysis have been so far adopted, namely:

1. Removal of one hemisphere. 2. Removal of both hemispheres. 3. Removal of all cerebellum or of one lobe and the opposite half of the cerebrum. 4. Removal of one hemisphere, combined with hemisection of the lower cervical spinal cord; (*a*) on the opposite side, and (*b*) on the same side as the lesion, and *vice versa*. 5. Division of the spinal cord.

The absinthe excitation in each group was made immediately after the operation, and also in all cases where possible after complete recovery from the shock—that is, on the following day, or at some subsequent date. The following are the results obtained in the cat.

1.—Removal of One Hemisphere.

Series A (1 to 11).—Absinthe excitation immediately after the operation. Results: General diminution of the intensity and duration of the fits. In a few cases the fits are unilateral, but in the majority the fit is bilateral. The fit on the injured side commences slightly after that on the sound side (not constant); the contractions are, as a rule, less powerful and less in number; there is a tendency to tonus rather than clonus. Preceding the death of the animal bilateral spasms (asphyxial spasms), accompanied with elevation of the tail and discharge of urine, is very frequent. The characteristic fits pass insensibly into the spasms, and, as they do so, the movements upon both sides tend to become more equal, or even to become more accentuated, upon the side of the lesion. The reflex excitability is greatly increased.

Series B (1 to 10).—In this series the left hemisphere was removed some days or weeks previous to absinthe excitation. The results are for the most part similar to those in the preceding group; the fits are more vigorous and simultaneous, and in many cases are equal on both sides. In these animals there was

rapid recovery after the operation, and "paresis" was only represented by a very slight awkwardness of motion. The intensity of the fits was in proportion to the recovery of action of the muscles of the weak side.

II.—Removal of Both Hemispheres.

(*a*) Removal of both hemispheres and immediate absinthe excitation (series 1 to 8). This produces complete arrest or prevention of the fits in the arms and legs. The face movements may be present. Reflex excitability and respiration is increased. There are bilateral asphyxial spasms. (*b*) Removal of both hemispheres, and absinthe excitation on the second day. In one well-marked case there were bilateral, powerful, slow, clonic spasms. (*c*) Removal of left hemisphere with subsequent removal of the right hemisphere and absinthe excitation (series 1 to 7). This produces arrest of the typical tonic and clonic fits, A small tonic contraction may be seen on both sides; in one case this was limited to the side first operated upon.

III.—Removal of the Cerebellum.

(*a*) Complete removal of the cerebellum and immediate absinthe excitation has been followed by typical fits. (*b*) (Series 1 to 8) When the left hemisphere and the right lobe of the cerebellum are removed at the one operation and absinthe is immediately given, there is marked unilaterality of the fits, clonus and tonus on the left side, and usually tonus with very slight clonus upon the right side. When the hemisphere is removed subsequent to the right lobe of the cerebellum there is marked unilaterality, strong clonic contractions on the left side, and slight tonus on the right side. The removal of the lobe of the cerebellum produces one-sided weakness. This agrees with Russell's observation in the dog.

IV.—Removal of One Hemisphere Combined with Hemisection of the Cord.

When hemisection is made in the cervical region subsequent to removal of the left hemisphere, there is complete arrest of the fits on the side corresponding to the hemisection, whether this be the right or left side.

V.—Section of the Cord.

Hemisections in the cervical region are followed by complete paralysis of the corresponding side; the paralysis, however, tends to become less, but is always, as far as observations go, much more marked than in the case of ablation of a hemisphere. In the same way the fit is at first unilateral; but later, and apparently depending upon the degree of recovery, there may be slight tonic and clonic manifestations upon the side of lesion. Complete division of the cervical spinal cord prevents the fits in the limb muscles, but there are clonic and tonic spasms of the face and shoulder muscles.

Conclusion.

In drawing conclusions from these experiments it must be remembered that there are not yet sufficient data to say what share the cerebellum may take in the production of the clonic spasms. Fits may occur in the absence of the cerebellum, but removal of one lobe of the cerebellum, coupled with that of the opposite cerebral hemisphere, tends to produce unilaterality. The question arises, therefore, concerning the auxiliary action of the cerebellum, and the experiments are not sufficient as yet to throw light on this point. That the cerebellum should exercise some influence seems probable from the symptoms which we know follow removal of portions of the cerebellum. The experiments show that one hemisphere, with an intact cerebellum, is capable of discharging impulses to both halves of the body, and they tend to show that one-half of the cord can conduct to both sides of the body. They show that the rhythmic clonic fits are not obtained where the hemispheres are absent, the cerebellum remaining intact. They show that the impulses may descend through other channels than the pyramidal tracts; this is shown by the fact that, after the removal of one hemisphere, the corresponding pyramid degenerates and atrophies, yet fits can be obtained on that side by absinthe, which are, however, immediately arrested by hemisection of the cord. The experiments further show that absinthe has an action upon the whole of the central nervous system.

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"An Experimental Investigation of the Nerve Roots which enter into the formation of the Lumbo-sacral Plexus of *Macacus rhesus*."

By J. S. RISIEN RUSSELL, M.B., M.R.C.P., Assistant Physician to the Metropolitan Hospital. Communicated by Professor V. HORSLEY, F.R.S. Received March 22,—Read May 18, 1893.*

(From the Pathological Laboratory, University College, London.)

CONTENTS.

I. Introduction.
II. Anatomical introduction.
III. Operative procedure.
IV. Division of the subject and analysis of results.
a. Division of the subject.
b. Analysis of results.
Part I.—Compound movements obtained by excitation of each whole nerve root.
Part II.—Minute differentiation obtained by excitation of the individual bundles of each nerve root.
Part III.—Direct observation (after dissection) of muscles thrown into action by excitation of the separate nerve roots.
Corollary to Part III.
Part IV (*Control*).—Alteration in the action of the posterior extremity in progression, in climbing or in standing, evoked by section of a nerve root.
Part V (*Control*).—Influence of section of a root or roots in excluding part of an epileptic spasm induced in the limb by intravenous injection of absinthe.
Corollary to Part V.
Discussion of results. Conclusions.

Introduction.

The first part of my task is to express my great indebtedness to Professor Victor Horsley for enabling me to carry out this investigation under favourable circumstances at the Pathological Laboratory of University College, and for his great willingness at all times to criticise the results which I obtained.

In a paper on the functions of the nerve roots which enter into the formation of the brachial plexus of the dog,† I gave an account of the views that have been expressed and the work done in connexion with the limb plexuses. The hypotheses as to their significance advanced by Reil,‡ Scarpa,§ A. Monro,‖ Sömmering,¶ and others were

* Part of the expenses connected with this research have been defrayed by a grant from the Scientific Grants Committee of the British Medical Association.

† 'Phil. Trans.,' 1892.

‡ 'De Nervorum Structurâ.'

§ 'De Gangliis et Plexibus

‖ 'Observations on the Structure and Functions of the Nervous System.'

¶ 'Anatom.,' Pars quinta.

not alluded to, as they were mere conjectures, unsupported by any substantial evidence. The works of Krause, Schwalbe, Herringham, and Paterson were quoted as evidence of how far the problems connected with this subject have been elucidated by anatomical investigation, and the observations of Erb, Knie, and Thorburn alluded to as showing what advance had been made in the subject by the study of diseased processes in man.

Our knowledge of this subject has been greatly increased by numerous experimental researches, the latest of which is that by Sherrington. As his work is of such recent date and contains a historical account of all previous experimental researches that have been carried out in connexion with the lumbo-sacral plexus, it would be superfluous for me to do more than give a list of references to the various communications on the subject, including that of Sherrington, which list will be found at the end of this paper.

Anatomical Introduction.

The Lumbo-sacral Plexus in the Monkey.

Forgue, who does not mention what class of monkey he is dealing with, represents in diagrammatic form the nerves with the roots from which they are derived as follows:—The anterior crural from the 4th, 5th, and 6th lumbar nerve roots; the obturator from the same roots; and the sciatic from the 5th, 6th, and 7th lumbar and the 1st sacral nerve roots. The 2nd sacral root is also figured as sending a branch to the 1st sacral root before the latter enters the sciatic.

Sherrington describes two chief types of plexus in the monkey (*Macacus rhesus*); what he calls a "postfixed" and a "prefixed." The former is figured as having the following arrangement. The external cutaneous takes its origin from the 3rd and 4th lumbar; the 3rd lumbar also sending a branch to the 4th before the latter enters the anterior crural and obturator nerves, which it does in conjugation with the 5th lumbar root, both nerves also obtaining a filament from the 6th lumbar, while the sciatic is represented as springing from the 6th and 7th lumbar and 1st and 2nd sacral roots.

The representation of the "prefixed" plexus shows the origin of the external cutaneous nerve to be the same as in the "postfixed" type, while the branch from the 3rd to the 4th lumbar root is represented as joining the latter after it has given its branch to the external cutaneous nerve. This branch from the 3rd to the 4th lumbar apparently is supposed to send fibres to both the anterior crural and obturator nerves; these nerves also receiving branches from the 4th and 5th lumbar roots. The sciatic is figured as formed from the 5th, 6th, and 7th lumbar and 1st sacral nerve roots.

That Forgue's representation of the arrangement of the plexus does

not agree wholly with either of the types figured by Sherrington is evident; but further comparison of the descriptions of the two observers is rendered useless by the fact that Forgue omits to mention the class of monkey he made his observations on.

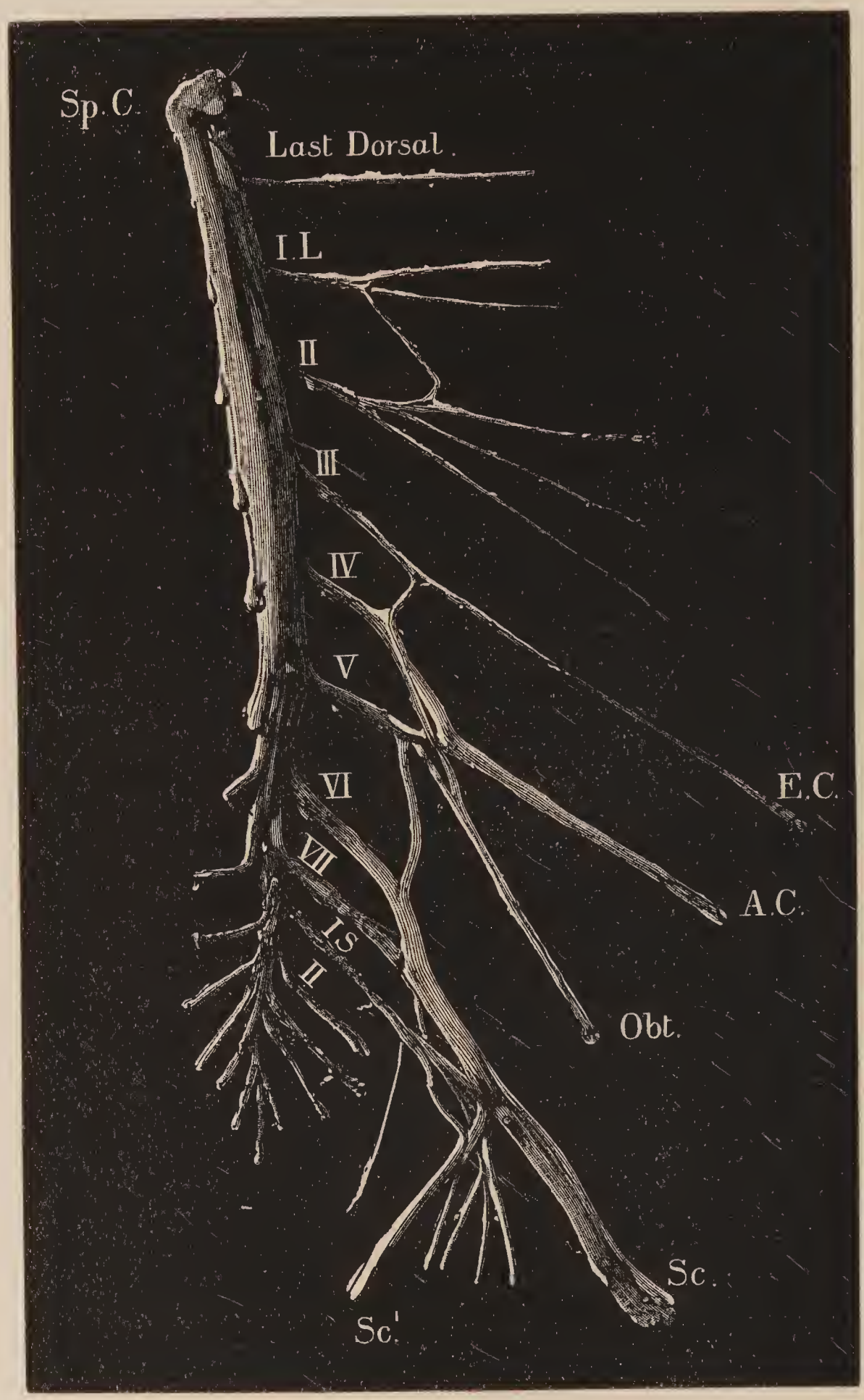
Like Sherrington, I confined myself to *Macacus rhesus* in my experiments on the lumbo-sacral plexus, and from numerous careful dissections, I am compelled to conclude that, at any rate in those animals dissected by me, one type occurred sufficiently frequently to make it necessary to look upon it as the chief one. But at the same time, among the different variations, one was conspicuously more frequent than any of the others, but scarcely sufficiently frequent, I think, to warrant my at present describing two main types, in the way that Sherrington has done.

The arrangement in what has been the most common type in the animals which came under my observation was as follows (see fig. 1) :—The external cutaneous received fibres from the 3rd and 4th lumbar roots; the anterior crural from the 4th and 5th, as did the obturator nerve; and the 6th received a branch from the 5th lumbar root, before its junction with the 7th lumbar root to form the sciatic, which nerve also received a branch from the 1st sacral root. As far as I have seen, the 2nd sacral nerve root never sends a branch to the sciatic, in this type of plexus.

The variation which I have spoken of above as being the most common has the following arrangement (see figs. 2 and 3) :—The external cutaneous is derived from the 3rd and 4th lumbar roots, as in the chief type; but the 3rd lumbar sends a branch to the 4th before the latter gives off its branches to the external cutaneous, the anterior crural, and the obturator nerves. The anterior crural then receives a branch from the 4th and another from the 5th lumbar roots, as in the chief type; but the obturator receives, in addition, a branch from the 6th lumbar root. The sciatic receives no branch from the 5th lumbar root, but only from the 6th and 7th lumbar and 1st sacral roots. I have been unable by the most minute dissections, aided by magnifying lenses, to trace any nerve fibres from the 2nd sacral root to the sciatic trunk. It will be thus seen that the chief points of difference between this and the most common type of plexus consist firstly in the absence of a branch from the 5th to the 6th lumbar root, and therefore to the sciatic; secondly, in the fact that the obturator nerve receives a branch from the 6th lumbar root in addition to those which it receives from the 4th and 5th lumbar; and, thirdly, in that the 3rd lumbar sends a branch to the 4th before the latter gives off any branches to the nerve trunks derived in part from it.

In the plexus of which fig. 2 is an example there can be no doubt that the 2nd sacral nerve root does not send a branch to the sciatic trunk, while that from which fig. 3 is taken shows how in some cases

Fig. 1.



it might easily be erroneously supposed to do so, and how, in such an arrangement, excitation currents might diffuse, with the greatest readiness, from the 2nd to the 1st sacral nerve root, and thus lead to fallacy.

Fig. 2.

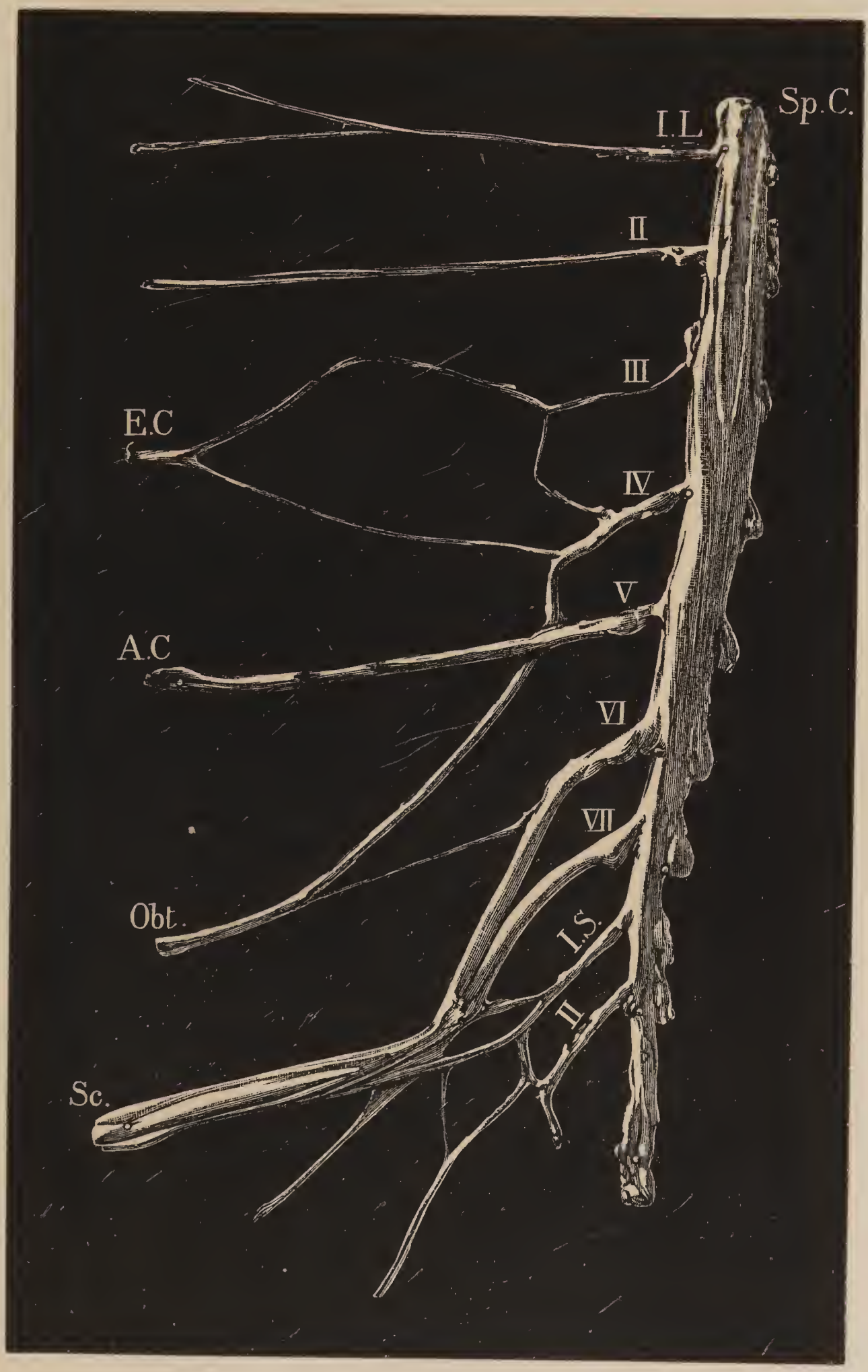
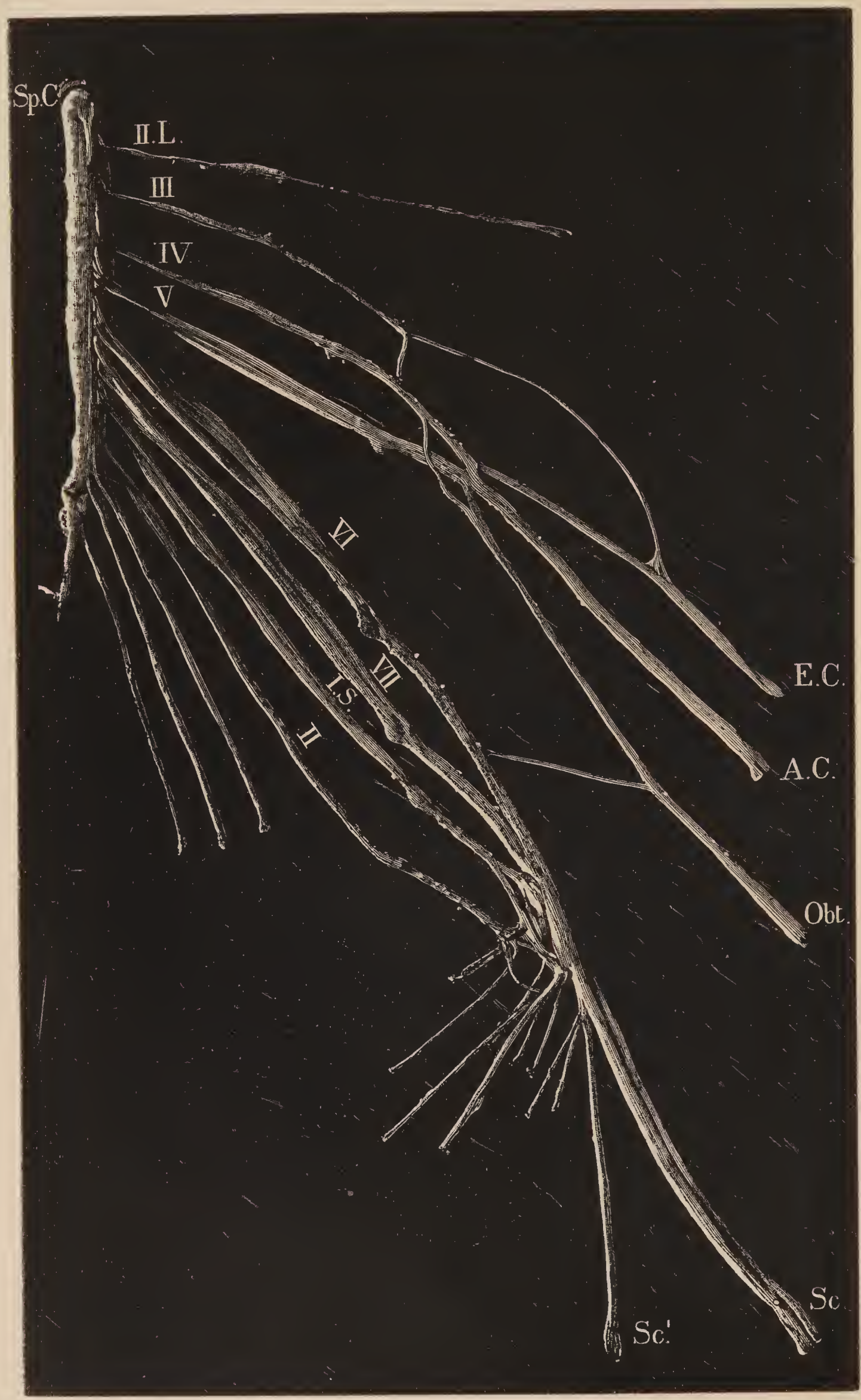


FIG. 3.



The similarity between the plexus which I have found most common and the "prefixed" plexus of Sherrington is obvious; but there is one point of difference. The branch figured by Sherrington as going from the 3rd to the 4th lumbar, and thus taking part in the formation of the anterior crural and obturator nerves, I have not found present. So, too, the variation which I have described as most common agrees with what he calls the "postfixed" type of plexus, with the exception that I have not found a branch from the 6th lumbar to the anterior crural; nor have I found that the 2nd sacral sends a branch to the sciatic. But the number of times I have met with this form of variation have not been sufficiently frequent to justify my denying the existence of such a branch as that from the 2nd sacral root to the sciatic. Indeed, its existence in some cases is rendered very probable by a comparison of this form of plexus with that most commonly met by me in the dog, which resembles it, and in which the 2nd sacral root sends a branch to the sciatic trunk. It is curious that in the species I have examined, the type of plexus most commonly met with in the dog should form the exception in the monkey, while that most commonly met with in the monkey should be the exception in the dog. The fundamental point of difference in the constitution of the two plexuses in the species I have examined has been the presence of a branch from the 5th to the 6th lumbar root in the one form of plexus, and its absence in the other, and it shows that the passage from the one type of plexus to the other is not an abrupt, but a gradual one, for, while in the majority of monkeys examined I found the branch from the 5th to the 6th lumbar root to be large, all graduations were met with down to the most minute filament connecting the two roots (see fig. 4).

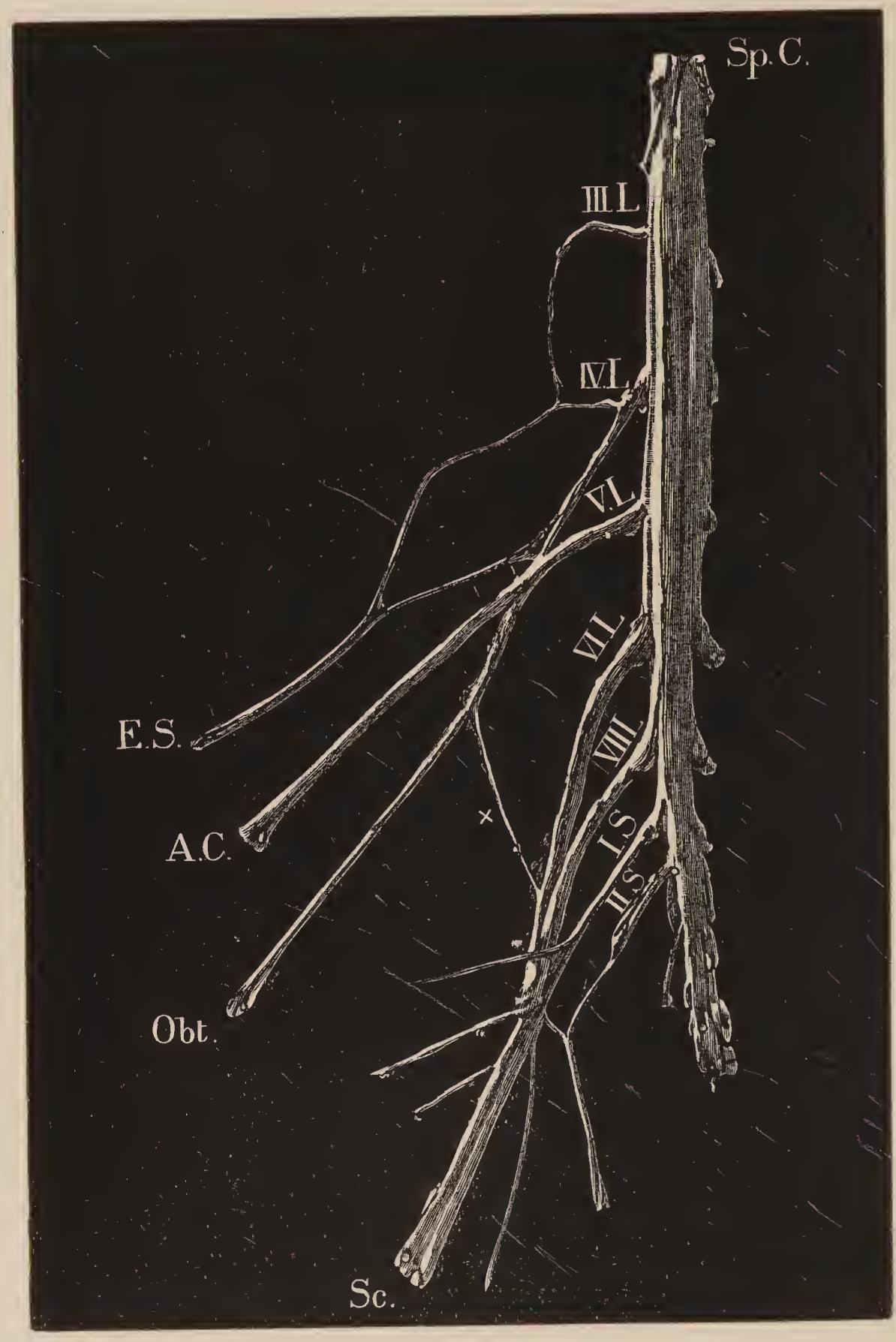
The Muscles of the Posterior Extremity of the Monkey, and their Actions.

In confirmation of Sherrington I find that the muscles of the posterior extremity of the monkey (*Macacus rhesus*) resemble very closely those met with in man; but a few points of difference exist, and must be briefly alluded to.

The gluteus maximus is a very thin flat muscle. There is no evidence of the existence of a peroneus tertius; but peroneo-tibialis muscle is sometimes present. The slip which the abductor hallucis in man occasionally sends to the first phalanx of the second digit is very large and constant, forming a separate muscle in fact.

As was explained in the paper on the brachial plexus of the dog, certain consequences of the action of the muscles deserve careful attention. In studying the mechanism by which the movements are brought about at the various joints, I found that a muscle might bring about a movement at a given joint upon which it has no direct

Fig. 4.



action, and I showed that this is due to the fact that certain muscles pass over more than one joint, and that they are not sufficiently long to allow of full movement taking place at one of those joints without their mechanically and passively pulling on their attachment on the other side of the other joint or joints. In the fore-limb this difficulty was chiefly encountered in connexion with the triceps, as when traction was made on this muscle, in addition to extension at the elbow joint, there resulted extension of all the lower segments of the

limb, owing to the arrangement of the muscles as has been explained above. So troublesome was this action when the movements at the wrist and digital joints were being studied, that an instrument was devised to exclude the action of the triceps under these circumstances. In the posterior extremity, the action of the quadratus femoris tends to produce, besides extension at the knee, extension at the ankle and of the digits. This action of the extensor muscle of the knee, though well marked in the dog, is much less so in the monkey, so that an assistant could fix the limb in such a position as to exclude this action without the aid of an instrument. It is obviously of great importance that this action of a muscle indirectly upon joints on which it has no direct action should be clearly recognised in all investigations of the movements at a given joint when any single nerve root is stimulated. If one muscle can directly or indirectly produce movements at so many joints, it is clear that we must first eliminate indirect effects of the action of this muscle before we can study the movements at these joints, as produced by the muscles which act directly on them, otherwise we should be led into error.

Operative Procedure.

a. Operation.—In every experiment the animal was narcotised by causing it to inhale ether; it was kept deeply under the influence of the anæsthetic during the whole of the experiment, and killed by an overdose of it at the end, except in those experiments in which the animals were allowed to live for some weeks for the study of the effect of section of nerve roots on its mode of progression and standing, and also to allow sufficient time for the degeneration in the peripheral nerves, consequent on such section of a nerve root, to develop. In these instances the operation, which was always a very trivial one, was done under strict antiseptic precautions, and the small wound afterwards dressed antiseptically. The animals were, of course, narcotised in these as in the other class of experiments. The neural canal was first opened, a ligature passed round the motor and sensory portions of a given nerve root together, as close to the spinal cord as possible, after which the two portions of the root were divided between the ligature and the cord. When the separate bundles of nerve fibres of which a nerve root is composed were under investigation, the whole root was dissected out to a varying distance beyond its point of exit from the neural canal, so as to allow of each separate bundle being separated from the others contained in a nerve root, for as long a distance as possible, in order to prevent diffusion of the current from one bundle of nerve fibres to another during the excitation experiments.

In those experiments in which the muscles were exposed by dis-

section, in order to allow of their being directly observed in action when a nerve root was excited, the spinal cord was always first divided transversely in the mid-dorsal region, so as to preclude all possibility of the animal's being conscious of any pain, a possibility most remote, seeing that it was always kept profoundly under the influence of the anæsthetic in this as in all other experiments on the nerve roots.

When intravenous injections of absinthe were given, a jugular or femoral vein was exposed, and a certain quantity of the essential oil injected into the vein selected, by means of a hypodermic syringe.

b. Excitation.—The distal portion of the divided motor root was separated from its sensory fellow, raised in the air by means of a ligature passed round it, and stimulated by means of fine platinum electrodes attached to the secondary coil of a du Bois Reymond's inductorium supplied by a bichromate cell. Exactly the same apparatus was used in excitation of the cortex cerebri (*vide infra*).

Division of Subject and Analysis of Results.

a. Division of the Subject.

As in the previous research, I approached the question by simple excitation of the peripheral end of the cut root, and observation of the compound movement thus produced forms the first part of the investigation. The next step was to carry out, if possible, a more minute analysis of this combined movement, dividing it into its component factors, *e.g.*, by using minimal currents of excitation, applied to the separate bundles of nerve fibres contained in the nerve root. The strength of current necessary to produce the maximum effect without diffusing to other nerve roots was found on the average to be 500 to 600 on Kronecker's inductorium scale. When minimum strengths of current were used for exciting the separate bundles of nerve fibres of which a nerve root is composed, the secondary coil stood at 40 to 50 on Kronecker's inductorium scale, on an average. But both these readings naturally varied considerably, according as the solution in the battery was fresh or old.

The way in which I was led to suppose that each separate natural bundle of nerve fibres of which a nerve root is composed might represent some simple movement, and that it might be possible to evoke such a simple movement by exciting these separate bundles of nerve fibres by minimal strengths of current, has been fully detailed in my former paper. This minute differentiation is not so easily carried out in the lumbo-sacral roots as was found possible in the cervico-dorsal roots of the dog, owing to the fact that the distance between the points of exit of the various nerve roots and those where they

combine to form the plexus is in most instances too small to allow of the minute bundles of nerve fibres being separated from each other for a sufficient length of their course. I was always able to differentiate several of the movements in each root, but was never able to differentiate all in any given root at the same operation. Another factor which contributes to make this process of minute differentiation so difficult is the delicacy of the nerve roots in the monkey as compared with those of the dog, as injury of the nerve fibres is more difficult to prevent in consequence, in the process of their separation from each other. With these difficulties to contend with, the process of differentiation of the various movements was aided by the division of muscles and tendons. That is, after it had been ascertained that a certain movement at a given joint resulted on excitation of a certain bundle of fibres, these muscles or their tendons were divided, and the same bundle of nerve fibres again excited in order to ascertain whether any other movement could be produced at the same joint, *e.g.*, after flexion at a joint had been produced, the flexor muscles acting on that joint were divided, in order to ascertain whether any fibres representing extension existed in the bundle of nerve fibres under investigation.

This minute differentiation forms therefore the second part of the investigation.

Thus far the investigation dealt with movements ; it was obviously necessary to pursue the matter further, and to see upon dissection what individual muscles were innervated by the various roots, or their parts when successively excited. This forms the third part of the work. As a corollary to this latter question, I have attempted to determine to what degree any given root supplies a muscle when the latter is innervated from more than one root, and whether any given muscle fibre is possibly supplied from more than one root.

The necessity of instituting new experiments in control of the results obtained by the foregoing methods led to the institution of the following procedures.

Of these, the first, constituting the fourth part of the investigation, consisted in dividing one or more roots, and then observing what effect was produced thereby in the direction of alteration of the natural gait or movement of the limb in progression and climbing.

Another control method, the results of which are embodied in the fifth part, was devised as follows:—A nerve root was divided (in some cases more than one), general epilepsy was then induced by intravenous injection of the essential oil of absinthe, and the resulting deficient participation in the fit of the limb in relation with the divided root or roots carefully observed.

As a corollary to this part of the subject, I tried whether the results obtained by the last method of experimentation are in any way altered when the root or roots are divided some weeks previously, instead of at the time when the epileptic spasms are induced.

*b. Analysis of Results.**

It was found most convenient and instructive to place together the results obtained in Parts I and II of the former investigation, and I see no reason for altering this method of description in detailing the following results.

Part I. Compound movements obtained by excitation of the whole nerve root.

Part. II. Minute differentiation obtained by excitation of the individual natural bundles of the nerve root.

1*st Lumbar Root.*—No intrinsic movement of the limb.

2*nd Lumbar Root.*—No intrinsic movement of the limb.

3*rd Lumbar Root.*—Slight flexion at the hip.

4*th Lumbar Root.*—Part I. Flexion at the hip, with the thigh adducted and the leg extended at the knee.

Part II. (1)†Flexion at the hip.
(2) Adduction of the thigh.
(3) Extension at the knee.

5*th Lumbar Root.*—Part I. Extension of the whole limb with adduction and internal rotation of the thigh and dorsiflexion of the foot.

Part II. (1) Adduction of the limb.
(2) Extension at the knee.
(3) Dorsiflexion of the foot.
(4) Extension of the digits.
(5) Extension of the hallux.

6*th Lumbar Root.*—Part I. The limb extended at the hip, adducted and rotated outwards; flexed at the knee, with the foot at right angles and everted at the ankle, the digits and hallux being flexed at the distal phalangeal joints.

* These results are based on a large number of experiments, and although variations were met with, the results which appeared to be the most constant are those given here.

† The small numbers in brackets denote the bundles from which a different movement was obtained when such bundles were separated in a nerve root. Only those bundles destined for the supply of muscles of the extremity are noted, which accounts in part for so few bundles being mentioned in connexion with some roots; but the variation in the size of the different roots is also responsible for this.

Part II. (1) Extension at the hip.
(2) Flexion at the knee.
(3) Dorsiflexion at the ankle.
(4) Extension at the ankle.
(5) Eversion of the foot.
(6) Extension of the digits.
(7) Flexion of the digits.
(8) Flexion of the hallux.
(9) Extension of the hallux.

7th Lumbar Root.—Part I. The limb extended at the hip, flexed at the knee, extended at the ankle, with the plantar surface of the foot looking inwards, the digits flexed at their metacarpo-phalangeal joints, and the hallux flexed and adducted into the sole of the foot, beneath the flexed digits.

Part II. (1) Extension at the hip.
(2) Flexion at the knee.
(3) Extension at the ankle.
(4) Flexion of the digits at their metacarpo-phalangeal joints.
(5) Flexion of the hallux.
(6) Adduction of the hallux.

1*st Sacral Root.*—Part I. Interosseal flexion of the digits, with flexion and adduction of the hallux.

Part II. (1) Flexion of the digits.
(2) Adduction of the hallux.
(3) Flexion of the hallux.

2*nd Sacral Root.*—No movement in the limb.

Part III. Direct Observation (after Dissection) of Muscles thrown into action by Excitation of the separate Nerve Roots.

I next attempted to ascertain as far as possible which muscles are thrown into action by stimulation of the several nerve roots. In exposing the muscles, great care was taken to separate them from each other, so that any communicated movement of one muscle to another should be avoided, as, unless this is done, it is sometimes difficult to be sure whether a particular muscle is contracting, or whether the movement observed in it is only communicated to it by an adjoining muscle which is in action.

Two plans were followed in this connexion. In one, each root was successively selected, and all the muscles in action on excitation of it were noted, while, in the other, a particular muscle, or group of muscles, was kept under observation while all the roots which contributed to the plexus were separately excited. Thus the results

obtained by the one method could be checked by those obtained by the other. In my former experiments I frequently was able to expose the muscles directly after the animal was killed, because the nerve roots, at the end of a prolonged experiment, retained their excitability for a considerable time, half an hour or more. In these experiments this plan has been abandoned, and exposure of the muscles during life alone relied on.

1st Lumbar Root.
No muscle related to the limb.

2nd Lumbar Root.
Psoas parvus.

3rd Lumbar Root.
Psoas parvus.
Psoas magnus.
Sartorius.

4th Lumbar Root.
Psoas magnus.
Iliacus.
Sartorius.
Adductor longus.
Quadriceps extensor.
Gracilis.

5th Lumbar Root.
Iliacus.
Gluteus minimus.
Adductor longus.
Adductor magnus.
Quadriceps extensor.
Gracilis.
Tibialis anticus.
Tibialis posticus.
Extensor longus digitorum.
Extensor proprius hallucis.
Tensor fasciæ femoris.

6th Lumbar Root.
Adductor magnus.
Hamstrings.
Soleus.
Gastrocnemius.
Tibialis anticus.
Tibialis posticus.
Extensor longus digitorum.

Flexor longus digitorum.
Peroneus longus.
Peroneus brevis.
Extensor longus hallucis.
Gluteus maximus.
Gluteus medius.
Gluteus minimus.
Pyriformis.
Obturator internus.
Obturator externus.
Gemellus superior.
Gemellus inferior.
Quadratus femoris
Popliteus.
Plantaris.

7th Lumbar Root.

Hamstrings.
Gastrocnemius.
Soleus.
Flexor longus digitorum.
Peroneus longus.
Peroneus brevis.
Flexor longus hallucis.
Adductor hallucis.
Interossei.
Gluteus maximus.
Gluteus medius.
Pyriformis.
Obturator internus.
Obturator externus.
Gemellus superior.
Gemellus inferior.
Quadratus femoris.
Popliteus.
Plantaris.

1*st Sacral Root.*

Intrinsic muscles of the foot.

Corollary to Part III.

In my former paper the question as to whether a single bundle of nerve fibres representing a single simple movement ever remains distinct in a nerve root during its course to the muscles it supplies without inosculating with other motor nerve fibres was considered,

and evidence in favour of an affirmative reply brought forward. The results which have been obtained in the present investigation have been in conformity with this view, so that I see no reason to alter the opinion formerly expressed.

A further point that was determined in this connexion was the question whether, when a muscle receives nerve fibres from more than one nerve root, both nerve roots supply nerve fibres to one and the same muscle fibre, and evidence was adduced to negative this possibility. The following evidence also negatives this view:—The peroneus longus muscle is supplied with nerve fibres from the 6th and 7th lumbar nerve roots, and the maximum contraction which can be evoked on excitation of the 6th root alone was greater than that evoked by stimulation of the 7th root alone; but neither effect was as great as when both roots were simultaneously excited. Another muscle chosen in order to test this point was the sartorius, which is supplied by the 3rd and 4th lumbar roots. When the 3rd root is excited with a minimal stimulus, the resulting contraction of the muscle is limited to its upper part, while similar excitation of the 4th root is followed by contraction of its lower part alone.

Part IV (Control). Alteration in the Action of the Posterior Extremity in Progression in Climbing or in Standing evoked by Section of a Nerve Root.

The following experiments were performed in order to observe the effect of division of one or more nerve roots on the movements of the limb during use in ordinary progression, climbing, &c. I observed the effects produced by division of a single nerve root, of two or three consecutive roots, and of two or three alternate roots on the same side. In no instance did I find that the division of a single nerve root was followed by any alteration in the movements of the limb, such as could be detected by running or climbing, twenty-four hours after the operation. A variable amount of paresis or paralysis of certain movements followed section of two or more nerve roots. Section of two consecutive nerve roots produced a greater effect than section of two alternate roots on the same side, an intermediate root being left intact. The effect in both these cases depended on the size of the roots divided, for even if the roots divided were two consecutive ones, and caused great impairment of any given movement, yet the effect noticeable would be much greater if the roots divided were large than if they were small, for the number of other movements weakened would be greater with large than with small roots. I have never found that the monkey's power of grasping the wire of its cage-house in climbing, after section of the 1st and 2nd sacral roots, has been impaired in such a manner as to be

detectable, but here again the experiment has not been repeated sufficiently frequently in the type of monkey in which, according to Sherrington, the 2nd sacral root supplies a branch to the sciatic nerve, which supplies the intrinsic muscles of the foot.

In no case did section of the 1st and 2nd lumbar roots cause any impairment in the movements of the limb, nor did section of the 2nd and 3rd in combination. When the 3rd and 4th lumbar roots were divided on the same side, flexion at the hip was greatly impaired. Movements at the knee appeared most affected when the 4th and 5th, or 6th and 7th, lumbar roots were divided together on the same side, roots which, as we have seen from the stimulation experiments, are concerned with the movements at the knee. The division of the last two roots mentioned also produced most effect on the movements at the ankle. The movements of the digits were most affected when the 7th lumbar and 1st sacral roots were divided together, roots excitation of which produced these movements. Section of the alternate roots, 3rd and 5th, 4th and 6th, 5th and 7th, 6th lumbar and 1st sacral, in combination, produced very little effect. In some cases it was possible to detect slight impairment of movements, but in others it was extremely difficult to be sure that there was any. If, however, three alternate roots, such as the 3rd, 5th, and 7th lumbar, or the 4th and 6th lumbar and 1st sacral, were divided together on the same side, there was no difficulty in detecting the general impairment of the movements of the limb.

In every case there was rapid improvement. In some this was so great that it was difficult to be certain that any impairment of movement remained, notably where alternate roots had been divided. In others, while most of the movements seemed as well performed as on the opposite side, impairment of a particular movement at a given joint remained, this being the case where two or more consecutive roots had been divided.

These results are in keeping with those which were obtained in connexion with the cervico-dorsal nerve roots of the dog. As in those experiments, reunion of the divided ends of the nerve roots was not the cause of the improvement in motor power, as there was not the slightest sign of any such reunion on post-mortem examination, and I have no other explanation to offer for the improvement in motor power which occurs, other than one of the hypotheses formerly advanced in explanation of the phenomenon. One of these suggested the possibility of a reflex inhibitory effect on the cells of the cortex cerebri by the section of a nerve root or roots, producing at first a greater degree of paralysis than would result from exclusion of the nerve root alone. The other supposed it possible that cortical impressions travelling down to the limb and meeting with a block, owing to the division of the fibres along which they formerly passed,

gradually become diverted, it may be through the anterior horn cells of the spinal cord, along other channels.

Part V (Control). Influence of Section of Root or Roots in excluding part of an Epileptic Spasm induced in the Limb by Intravenous Injection of Absinthe.

In this series of experiments an attempt was made to obtain further information as to the functional relations of the nerve roots to the muscles they supply, by the following method of experimentation. A nerve root was first exposed, but not divided; either a jugular or femoral vein was exposed, and 2 minims of the essential oil of absinthe injected into the vein by means of a hypodermic syringe. In order to evoke subsequent epileptic attacks in the same animal, doses of 1 minim of the oil of absinthe were found sufficient. In some cases, after several injections of absinthe, the excitability of the cortex became sufficiently increased to allow of general epilepsy being evoked by means of the induced current applied to the motor area of the cortex cerebri, a method which rarely succeeds in evoking general epilepsy in the monkey under other circumstances.

The first observation that was made in every instance was one to determine the position assumed by the limb during the general convulsions which followed the introduction of absinthe into a vein. In this way it was easy to exclude any error due to injury of any of the roots during the operation necessary to expose them. The position which the limb assumed when all the nerve roots were intact was one of flexion of thigh on the abdomen, with the leg at right angles to the thigh at the knee joint, the foot dorsiflexed at the ankle, and the digits flexed.

When the 3rd lumbar root was excluded, the position assumed by the limb was the same as on the opposite side on which all the roots were intact, with the exception of the flexion of the thigh on the abdomen being less pronounced.

Exclusion of the 3rd and 4th lumbar roots allowed extension at the hip to predominate over flexion, a result in keeping with the fact that excitation of both these roots produced flexion at this joint; while exclusion of the 5th lumbar root as well allowed flexion at the knee to predominate more markedly over extension. After section of the 6th lumbar on the same side, there was only feeble flexion at the knee, with extension instead of dorsiflexion of the root and flexion of the digits. The only intrinsic movement of the limb during general convulsions when the 7th lumbar was also divided was adduction and flexion of the hallux and flexion of the digits, movements which we have seen resulted on excitation of the 1st sacral root; and when

this root was also divided no intrinsic movement of the limb could be observed during the cortical discharge.

On excluding the 1st sacral root alone on one side, no tangible difference in the positions of the limbs on the two sides could be detected during the general convulsions evoked by absinthe.

Exclusion of the 7th lumbar alone caused an increase of flexion at the hip on that side, owing to the extensors being weakened, while there was more extension and less flexion at the knee, because the hamstrings are represented in this root, marked tibial dorsiflexion at the ankle, as the extensors were enfeebled, and flexion of the digits at the phalangeal joints. When the 1st sacral was divided in conjunction with the 7th lumbar root, the limb assumed exactly the same position as in the last experiment, except that the digits were not so powerfully flexed, and the hallux was not adducted, movements which excitation of these roots evoke. The marked feature which was noticeable after division of the 6th lumbar root, in addition to the two last mentioned, was that there was no sign of movement of the digits or hallux during the convulsions, because, of course, all the roots excitation of which produced movements of these parts were divided.

Combined section of the 5th, 6th, and 7th lumbar roots allowed of flexion at the hip, feeble extension at the knee, and flexion at the digits, with adduction at the hallux, during the cortical discharge. The foot remained quite motionless at the ankle joint, as was to be expected, seeing that excitation of no nerve root other than these produced movement at this joint.

Alternate roots were divided in the following combination, and the position of the limb observed during general convulsions. The 4th and 6th lumbar roots divided together caused flexion at the hip to be less marked, as was flexion at the knee, dorsiflexion at the foot, and flexion of the digits. There was thus a weakening of all the movements which predominated when all the roots were intact.

Section of the 5th and 7th lumbar roots, at the same time, was responsible for more marked flexion at the hip and knee and dorsiflexion of the foot. So that, although one of the roots which supplies the quadriceps extensor and one of those which supplies the hamstrings was divided, the section of that to the former group of muscles was attended with the greater result, for it allowed the remaining flexor root to predominate, so to speak, over the remaining extensor root to a greater extent than did the two flexors over the two extensors before any of the roots were divided.

Corollary to Part V.

It seemed desirable to test carefully the question as to whether section of a root or roots some time previous to that at which the

general convulsions were evoked is attended with the same results as when the section is done at the time when the convulsions are induced. I accordingly divided the 4th and 6th lumbar roots on one side, ten days before the day on which I proposed to excite the cortical discharge; and I divided the same roots on the opposite side at the time when the general convulsions were evoked. The result was that the positions of the two limbs were identical during the convulsions. The result of this experiment was confirmed by similar experiments with different combinations of nerve roots.

This method of experimentation was first employed by me in the investigation of the nerve roots which enter into the formation of the brachial plexus of the dog; and, as I have before pointed out, it serves the double purpose of being a means of checking the results of direct stimulation experiments, and of affording us the power of ascertaining whether elimination of a root does or does not result in incoordination of the remaining combination of movements. The results obtained by its use have abundantly confirmed those obtained by stimulating the individual nerve roots; and also prove that the coordination of the movement produced by the remaining roots is not in the slightest degree affected by the elimination of one or more of them. They also make it clear that there cannot be overflow of nerve impulses through the spinal centres, at any rate to any great extent, *i.e.*, impulses which should reach the muscle through the nerve root that has been divided do not under these circumstances reach them by other commissural channels.

Discussion of Results. Conclusions.

Stimulation Experiments.—A comparison of the results obtained by Ferrier and Yeo, those by Sherrington, and my own, shows that there is considerable difference of opinion as to which is the highest nerve root in the lumbar series excitation of which produces movement in the posterior extremity of the monkey. We are all agreed that flexion at the hip is the first movement of the limb evoked as we excite the lumbar roots from above downwards, but Ferrier and Yeo regarded the 4th lumbar as the first in the series from above down excitation of which caused this movement, whilst Sherrington states that in both types of plexus which he has described this movement was produced by excitation of the 2nd lumbar root, though it was feeble in the case of the "postfixed" class of plexus. In no instance have I observed this movement when the 2nd lumbar root was stimulated, the 3rd lumbar being the first root in the series from above down in which I have observed this movement to be represented.

Extension at the hip Ferrier and Yeo found represented in the 5th

lumbar root, while Sherrington and I have found the 6th lumbar root to be the first from above in which the movement is represented.

Extension at the knee Sherrington places as high as the 3rd lumbar root, while my own observations coincide with those of Ferrier and Yeo, who found the 4th lumbar to be the highest root in which this movement is represented.

We are all agreed that flexion of the knee is first represented in the 6th lumbar root from above, though Sherrington has also found it represented as high as the 5th lumbar root; rarely in the "prefixed" class of plexus, which resembles most the type of plexus I have most commonly met with.

Ferrier and Yeo do not mention dorsiflexion at the ankle as produced on excitation of any nerve root, while Sherrington and I are agreed that the 5th lumbar is the highest in the series in which this movement is represented.

We have all found extension at the ankle to be first represented in the 6th lumbar root from above; but, while Ferrier and Yeo and I find flexion of the hallux and digits first represented in the 6th lumbar root, Sherrington states that it is first represented in the 5th.

With regard to the inferior limit of supply to the limb, Ferrier and Yeo found this to correspond to the 1st sacral nerve root, and this has been the lowest root of the series from which I have been able to obtain any response in the limb.

Sherrington found that in the "prefixed" class of plexus which he has described, this is the lowest limit of root supply to the limb; but that in the "postfixed" class this limit extends as low as the 2nd sacral nerve root (9th post-thoracic root).

The number of times I have met with the type of plexus most resembling that described as "postfixed" by Sherrington has not been sufficiently frequent to justify my expressing any decided opinion as to the inferior limit of root supply to the limb in this class of plexus. All I can say is that I have never succeeded in evoking any intrinsic movement in the limb by excitation of the 2nd sacral root with currents of such strength as elicited movement when applied to other nerve roots, or even with currents very much stronger than this. Only by using such powerful currents that there could be no doubt as to the diffusion of the current beyond the root to which it was applied, was I ever able to elicit any intrinsic movement in the limb. Further, I have failed, by most careful minute dissections, aided by powerful lenses, to trace any nerve fibres from the 2nd sacral nerve root to the sciatic nerve. Of course the crucial test of this point would be to divide the 2nd sacral nerve root in this class of plexus, and observe whether degeneration in the sciatic nerve follows. This I have attempted, but unfortunately the animals in

whom I have divided the 2nd sacral nerve roots have, up to the present, had plexuses resembling the "prefixed" class. I have great difficulty in understanding how Sherrington finds any given muscle represented in so many more nerve roots, as a rule, than I do, and, conversely, how he finds so many more muscles, and, in consequence, movements, represented in certain roots. As an instance, the tibialis anticus is stated to be represented in the 5th, 6th, and 7th lumbar nerve roots, while I have only found it represented in the 5th and 6th lumbar roots. Then, again, the 1st sacral nerve root in the "prefixed" class of plexus, which corresponds most closely to the type of plexus I have most commonly met with, is said to produce extension at the hip with slight rotation outward of the thigh, flexion at the knee, extension at the ankle, strong flexion and abduction of the hallux and flexion of the digits in "interosseous" position; whereas, like Ferrier and Yeo, the only movements I have found most constantly represented in this root have been interosseal flexion of the digits, with flexion and adduction of the hallux.

The only way in which I can account for these very great differences in our results is by supposing that while I have only included those roots in which a given muscle is most commonly met with, and those movements, or muscles, most commonly met with in any given root, Sherrington has included every variation; for, as an example, all the movements mentioned by him as represented in the 1st sacral root, I have found represented in that root in rare instances, but never all represented together in any single animal. The movements most commonly met with in any single animal were those already mentioned, and when variation occurred it consisted in one or other of the other movements being added to these.

If I am correct in my interpretation of Sherrington's classification of results, I cannot help feeling that that which I have adopted is more instructive and less likely to lead to confusion.

With regard to the question whether the limb plexuses have an anatomical or physiological significance, I find it difficult to believe that the developmental processes which bring about these arrangements of nerve fibres do so on a purely anatomical basis without regard for physiological combination. Because excitation of a given nerve root with the induced current evokes a movement which may not resemble a natural one is to me no argument against the possibility that in this nerve root nerve fibres destined for the supply of certain groups of muscles are combined in such proportions as they are likely to be required in certain natural movements. The point is one which is exceedingly difficult to test by experiment, and those instituted by Sherrington with a view to solving this problem do not appear to me to be conclusive.

The facts that muscles or groups of muscles are represented in such

different degrees in different nerve roots, and that one group predominates in one root while another predominates in another, lend strong argument to the probability that the arrangement is in great measure a functional one. If the arrangement of nerve fibres in the nerve roots is a purely anatomical one, why should all the fibres destined for the supply of a given muscle not be contained in the same nerve root? What necessity would there be for the division of the fibres so that one set of them should be contained in one root, while another set is contained in another? These points are strongly opposed to the supposition that such an arrangement has been brought about without any regard for physiological action. Then, also, the fact that muscles which are known to act in consort are represented in the same nerve root is one which it is difficult to interpret by mere anatomical arrangement without regard for physiological laws.

Contrary to the observations of Sherrington, I find that the compound effect obtained on electrical excitation of a nerve root may be resolved into its component factors, when it is found that movements diametrically opposed to each other may be represented in the same nerve root, *e.g.*, flexion and extension.

It seems to me that some of Sherrington's own results point in this direction; for although he makes the statement that each small bundle of nerve fibres in a nerve root represents a miniature root, as it were, yet he finds that by using minimal currents differentiation was obtained in so far that one simple movement was elicited before another as the current was gradually increased in strength. The explanation I would offer for the different conclusions come to on this point by this observer and myself is that he excited the nerve fibres on the proximal side of the intervertebral foramina while I excited them on the distal side. The latter procedure makes it possible to separate the different bundles of nerve fibres contained in a nerve root for a greater distance of their course, and thus to avoid more effectually the possibility of diffusion of the current from the bundles of fibres actually excited to those juxtaposed. I am aware, from my own experience, that it is almost impossible to get any differentiations of movements in a nerve root unless the bundles of fibres of which it is composed be first traced well beyond the intervertebral foramen. That this should be the case is only natural, for what is more likely than that the fibres, packed together so closely as are the bundles of a nerve root in their passage through an intervertebral foramen, should make it very easy for the current applied to one set of fibres to diffuse to others in such close contiguity. That separation of one bundle of nerve fibres from another for a sufficient distance in their course is as important a factor in this differentiation of simple movements as is the use of minimum currents for excita-

tion in this connexion, is proved by the difficulties met with in obtaining differentiation in the case of the nerve roots which enter into the formation of the lumbo-sacral plexus, where the distance between the points of exit of the nerve roots from the neural canal and the point where they unite to form the plexus is not so great as in the case of the cervico-dorsal roots and the brachial plexus, and where, consequently, differentiation is not so easy to effect as in the latter case. If further proof were needed in support of the fact, which I have repeatedly convinced myself and others of, viz., that it is possible to separate the fibres concerned with one simple movement in a nerve root from those concerned with another simple movement, nothing could be more convincing than the results which I obtained with regard to the recurrent laryngeal nerve.* In this small nerve I found that it was possible to separate those nerve fibres concerned with abduction from those concerned with adduction of the vocal cords; so that electrical excitation of the one set of fibres evoked the one movement, while excitation of the other set evoked the other movement. If such differentiation be possible in a nerve of such small size, how much the more likely is it that it should be possible in a nerve root of so much greater proportions; unless it is argued that the structural arrangement of nerve fibres in a nerve root differs from that met with in a nerve trunk. My own observations leave no doubt in my mind that the structural arrangement in a nerve root is identical with that met with in a nerve trunk; and there is, besides, abundant proof of this from the observations of others.†

Such single simple movements bear an almost constant relation to the nerve roots, the same movements being, as a rule, found in any given root, and such movements always bear the same relation to the spinal level, *e.g.*, extension and flexion of the knee are represented together in one root, while extension is represented alone in the root immediately above this, and flexion is represented alone in the root immediately below this.

Each bundle of nerve fibres, representing a single simple movement in a nerve root, remains distinct in its course to the muscle or muscles producing such a movement, without inosculating with other motor nerve fibres. Additional evidence in support of this statement is supplied by the results obtained in the case of the recurrent laryngeal nerve, for in this nerve it was found possible to separate accurately the abductor from the adductor fibres, and to trace them by dissection to the abductor or adductor muscles of the larynx. And when one set of nerve fibres was divided while the other was left

* 'Roy. Soc. Proc.,' vol. 51, 1892.

† *Cf.* Herringham, Paterson, &c.

intact, degeneration resulted in the muscles of corresponding function, and in these alone: those of opposite function showing no sign of degeneration.

The group of muscles supplied by any given nerve root occupy both the anterior and posterior surfaces of the limb;* in other words, muscles whose unimpeded action would produce one movement are represented in the same root as others whose action would produce a movement diametrically opposite, *e.g.*, the flexor and extensor muscles of the ankle are represented in the same nerve root. In such combinations certain muscles are always more extensively represented than others; so that, with a current sufficiently strong to stimulate all the fibres in a nerve root equally, certain muscles predominate in their action over others. The 6th lumbar root contains fibres which supply the flexors of the digits and fibres which supply the extensors, and yet when the whole of the fibres in the nerve root are simultaneously and equally excited flexion of the digits is brought about owing to the flexor muscles predominating over the extensors. This predominance of one group over another does not always obtain, however, as in the case of the ankle joint, where both the flexors and extensors are supplied by nerve fibres derived from the 6th lumbar root; simultaneous and equal excitation of all the fibres contained in this root causes the foot to be fixed at right angles at the ankle, neither the flexors nor the extensors predominating, but the one set of muscles equalising the action of the opposite set.

When a certain group of muscles is found to predominate in its action in one root it, as a rule, predominates in that root, *e.g.*, I have not met with an instance in which the flexors of the digits did not predominate over the extensors in their action when the 6th lumbar nerve root was stimulated.

If the muscles producing flexion of a certain joint predominate in their action in one root, those producing extension predominate in another. This does not, of course, apply only to when both the opposing groups of muscles are represented in two nerve roots, but also when they are represented in different nerve roots. We have seen, for instance, that in the case of the ankle joint the muscles producing dorsiflexion are represented in the 5th and 6th lumbar nerve roots, while those producing extension at the same joint are represented in the 6th and 7th lumbar roots. This being the case, dorsiflexion results on excitation of the 5th lumbar root, and extension results on excitation of the 7th.

When two opposed movements are represented in three consecutive nerve roots, the middle root of the series is that in which both movements are represented, while the root above contains the one movement and that below contains the other. Sometimes the two move-

* *Cf.* Patterson, Forgue, &c., *loc. cit.*

ments represented in the middle root of the series cancel each other, as it were, so that neither predominates, as in the case of flexion and extension at the ankle as represented in the 6th lumbar root. But when the muscles producing the one movement predominate over those producing the opposite one, in my experience those muscles always predominate in that root, *e.g.*, the flexors of the digits in the 6th lumbar root.

As regards the order in which flexion and extension at the various joints are represented in their relationship to the spinal level, we find the following to be the order in the fore limb of the dog.

Flexion at the shoulder.*
Flexion at the elbow.
Extension at the shoulder.
Extension at the wrist.
Flexion at the wrist.
Extension at the elbow.
Extension at the digital joints.
Flexion at the digital joints.

Thus, while flexion is represented at a higher level than extension for the upper segments of the limb, the reverse obtains for the lower segments of the limb.

The following is the order of representation of these movements as regards the spinal level in the posterior extremity of the dog and monkey :—

Flexion at the hip.
Extension at the knee.
Flexion at the ankle.
Extension at the digital joints.
Flexion at the knee.
Extension at the hip.
Extension at the ankle.
Flexion at the digital joints.

Here the arrangement as regards the segments of the limb is an alternate one, flexion of the highest segment coming first, then extension of the next segment; while for the lower segments flexion again comes first, and is followed by extension for the next or terminal segment of the limbs.

So that in comparing the order of representation of movements of the posterior with that of the anterior extremity it is found that the highest segments coincide by having flexion as the highest representation, but that none of the other segments thus coincide, until the

* For purposes of comparison the forward movement of the limb at the shoulder joint is called flexion, while the backward movement is called extension.

terminal segments are reached, when extension is represented at a higher level than flexion in both instances. This is, however, not strictly accurate, for dorsiflexion at the ankle is strictly analogous to extension at the wrist; which leaves two joints alone at which there is any discord, viz., the elbow and knee.

It is possible by stimulation of a single bundle of fibres in a nerve root to produce contraction of a single muscle and it alone; but this effect is easier to obtain in the case of the cervico-dorsal roots which enter into the formation of the brachial plexus than it is in the case of the roots which combine to form the lumbo-sacral plexus, owing to the difficulty of isolating the separate bundles of nerve fibres of which the roots are composed for a great enough distance of their course after their exit from the neural canal, and before they unite to form the plexus in the case of the lumbo-sacral roots. The same muscle is always represented in more than one nerve root, usually two, and to an unequal extent in these. The only muscle which I have met with which is not represented in more than one nerve root is the tensor fasciæ femoris; and this agrees with Sherrington's observations with regard to this muscle. In coming to the conclusion that the rule is that a single muscle is represented in neither more nor less than two nerve roots, I wish it to be clearly understood that this conclusion is based upon the results obtained in any single individual of a class under observation. That, owing to variations, the same muscle may be found represented in three or even four nerve roots, I do not pretend to deny; but what I contend is that in the majority of instances a single muscle is represented in two nerve roots, and that when a variation is met with with regard to this muscle, it is, as a rule, that one of the nerve roots in which it is represented is different, rather than that it is represented in more nerve roots.

When the same muscle is represented in two nerve roots the muscle fibres innervated by one root are not innervated by the other; so that only part of the muscle contracts when a single root is excited. This part of the muscle may be either one end of it, one lateral half of it, or a superficial or deep part of it, as the case may be.

Ablation Experiments.

Division of any given nerve root produces paresis of the group of muscles supplied by it, which paresis is temporary, nearly all of it being recovered from. The amount of paresis or paralysis produced is proportional to the number of nerve roots divided; and this again varies according to whether the roots divided are consecutive or alternate ones, the effect being much greater in the former than in the latter case. That such should be the case is only what was to be expected, for section of any two consecutive roots cannot fail to cause

paralysis of certain muscles, if my observations with regard to the representation of muscles in the nerve roots are correct; whereas section of alternate roots, while causing paresis of more muscles, cannot produce paralysis of any one, the tensor fasciæ femoris being excepted. Such division of one or more nerve roots does not result in incoordination of the remaining muscular combinations represented in other nerve roots; the remaining movements are merely more feeble.

Exclusion of a certain Root or Roots during an Epileptic Spasm in the Limb.

Division of one or more nerve roots produces alteration of the position of a limb during an epileptic spasm, which altered position depends on the muscular combinations that have been thus thrown out of action. And the effect is identical when the root or roots are divided at the time that the convulsions are evoked, and when they have been divided some weeks previously, *i.e.*, the position assumed by the limb on one side of the body in which the root or roots are divided previously is identical to that assumed by its fellow of the opposite side, the root or roots of which are divided at the time that the convulsions are induced. No incoordination is produced in the action of the remaining muscular combinations; and there is no evidence of overflow of the impulses which ought to travel down the divided root into other channels through the spinal centres so as to reach the muscles by new paths.

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DESCRIPTION OF FIGURES.

Fig. 1.—From a photograph of the most common type of lumbo-sacral plexus met with in *Macacus rhesus*. Shows the lumbo-sacral cord, the nerve roots which

spring from one side of it, and the nerve trunks derived from these nerve roots. The 5th lumbar root sends a branch to the sciatic nerve in this type of plexus, and both the obturator and anterior crural nerves are derived from the 4th and 5th lumbar roots. The branch which appears to spring from the 3rd lumbar root and to pass to the 4th lumbar root, in the figure, is in reality a branch which has its origin from the 4th lumbar root, and which, together with the 3rd lumbar root, forms the external cutaneous nerve.

Sp.C. = Spinal cord.
I.L. = 1st lumbar nerve root.
I.S. = 1st sacral nerve root.
E.C. = External cutaneous nerve.
A.C. = Anterior crural nerve.
Obt. = Obturator nerve.
Sc. = Sciatic nerve.
Sc.′ = Division of sciatic nerve which supplies the hamstring muscles.

Fig. 2.—From a photograph of the type of lumbo-sacral plexus which is the most common variation met with in *Macacus rhesus*. The lumbo-sacral cord is represented with the nerve roots which arise from one side of it and the nerve trunks which have their origin from these nerve roots. The 5th lumbar root does not send a branch to the sciatic nerve, nor does the 2nd sacral nerve root do so. The obturator nerve receives a slender branch from the 6th lumbar root in addition to those derived from the 4th and 5th lumbar roots. The anterior crural nerve is formed from the 4th and 5th lumbar roots, while the external cutaneous is formed from the 3rd and 4th lumbar roots; and the 4th lumbar root receives a branch from the 3rd lumbar root, before it gives off any of its own branches.

Sp.C. = Spinal cord.
I.L. = 1st lumbar nerve root.
I.S. = 1st sacral nerve root.
E.C. = External cutaneous nerve.
A.C. = Anterior crural nerve.
Obt. = Obturator nerve.
Sc. = Sciatic nerve.

Fig. 3.—From a photograph of a lumbo-sacral plexus of *Macacus rhesus* of the same type as the last, intended to show how in some instances the 2nd sacral nerve root might be erroneously supposed to send a branch to the sciatic nerve, a fallacy which can only be avoided by more minute dissection.

Sp.C. = Spinal cord.
II.L. = 2nd lumbar nerve root.
I.S. = 1st sacral nerve root.
E.C. = External cutaneous nerve.
A.C. = Anterior crural nerve.
Obt. = Obturator nerve.
Sc. = Sciatic nerve.
Sc.′ = Division of sciatic nerve which supplies the hamstring muscles.

Fig. 4.—From another photograph of the most common type of lumbo-sacral plexus met with in *Macacus rhesus*, chiefly meant to show how slender the branch from the 5th to the 6th lumbar nerve root is in some cases.

Sp.C. = Spinal cord.
III.L., IV.L., V.L., VI.L., VII.L. = 3rd to 7th lumbar nerve roots.
I.S., II.S. = 1st and 2nd sacral nerve roots.
E.C. = External cutaneous nerve.
A.C. = Anterior crural nerve.
Obt. = Obturator nerve.
Sc. = Sciatic nerve.
× = Branch from 5th to 6th lumbar nerve root.

HARRISON AND SONS, PRINTERS IN ORDINARY TO HER MAJESTY, ST. MARTIN'S LANE.

[*From the* Proceedings of the Royal Society, Vol. 53.]

"On Some Circumstances under which the Normal State of the Knee Jerk is altered."* By J. S. Risien Russell, M.B., M.R.C.P., Assistant Physician to the Metropolitan Hospital. Communicated by Professor Victor Horsley, F.R.S. Received March 3, 1893.

(From the Pathological Laboratory of University College, London.)

CONTENTS.

1. Introduction.
2. History of Previous Experimental Work.
3. The General Plan of the Present Research.
4. Operative Procedure.
5. The Effects of Asphyxia.
6. The Effects of the Inhalation of certain Gases.
7. The Action of Ether and of Chloroform.
8. The Effects of Anæmia of the Spinal Centres.
9. The Action of Intravenous Injections of Absinthe and of Strychnia.
10. The Results of Section of the Spinal Cord.
11. The Effect of Removal of a Cerebral Hemisphere.
12. The Immediate and Late Effects of Extirpation of portions of the Cerebellum.
13. On Extirpation of the Labyrinth (control).
14. On Intracranial Section of the 8th Nerve (control).
15. On Chemical Irritation of the 8th Nerve (control).
16. Summary and Conclusions.

Introduction.

For the inception of the following work, which it is hoped will add some further facts to our knowledge of the most important of the "deep reflexes," the knee jerk, I am greatly indebted to the very kind suggestions of Dr. Hughlings-Jackson. To him I owe my best thanks for proposing the question of the influence of the asphyxial

* Part of the expenses connected with this experimental investigation have been defrayed by a grant from the Scientific Grants Committee of he British Medical Association.

state on the knee phenomenon, as a subject likely to be fruitful. The adoption of his early advice led to the investigation of many other points of noteworthy interest. I am also much obliged to Professor Horsley for suggestions, especially with regard to control experiments and operative procedures.

Since Brown-Séquard* described the condition expressed by him under the term spinal epilepsy, the so-called deep or tendon reflexes have attracted considerable attention, and have been the object of numerous investigations.

Charcot and Vulpian† were the first to accurately describe the phenomenon known as ankle clonus.

Bouchard‡ next observed the arm reflexes, and Erb§ and Westphal simultaneously directed their attention to the contraction of the quadriceps extensor which follows percussion of its tendon. Erb looked on the phenomenon as a reflex, while Westphal considered it the result of direct excitation of the muscle percussed or pulled at its extremity.

Joffroy endeavoured to prove that cutaneous excitation often evoked the phenomenon, and this view was not refuted until it was shown that it could be evoked in animals by percussion of the denuded tendon.

Westphal pinched, pricked, and irritated the skin in various ways without producing the knee jerk; a fold of skin lifted away from the tendon and subjected to blows with a hammer was attended with a like negative result. On the other hand, when the skin lying over the ligamentum patellæ was frozen by means of Richardson's process the contraction which followed a blow on the tendon was in no way lessened; nor was it where cutaneous anæsthesia existed in non-tabetic cases.

It soon became evident to observers that the knee jerk is a normal phenomenon, while ankle clonus is only met with in association with abnormal states; but there was some discrepancy of opinion as to whether the knee jerk is always present in healthy subjects. Berger‖ noted its absence in 1·567 per cent. of normal individuals; while in over 200 instances Eulenberger¶ never failed to elicit it in the newly born at various ages, and Gowers** states that it is probably never absent in health.

* 'Journ. de la Physiol.,' vol. 1, p. 475, 1858.

† 'Soc. Méd. des Hôp.,' May, 1866; 'Union Méd.,' p. 464, 1866.

‡ 'Arch. de Méd.,' vol. 2, p. 290, 1866.

§ 'Arch. f. Psych. et Nerven.,' vol. 5, p. 792; *ibid.*, vol. 5, p. 803, 1874; 'Comptes Rendus et Mém. de la Soc. de Biol.,' Series VI, vol. 2, p. 61, 1875.

‖ 'Centralbl. f. Nervenheilkunde,' 1879.

¶ 'Correspondenz-Blatt f. Schweizer. Aerzte,' Nos. 1 and 2, 1879.

** 'A Manual of Diseases of the Nervous System,' 2nd Ed., vol. 1, p. 431.

Westphal* connected for the first time the absence of the phenomenon with sclerosis of the posterior region of the lumbar cord, and Petitclerc† showed that it is also absent when the anterior roots of the spinal nerves are affected. It was about this time that Buzzard‡ called attention to the fact that in conditions where the knee jerk is absent the response of the vastus internus muscle to direct percussion may be actually more brisk than in health.

Exaltation of the tendon reflexes was recognised by numerous observers as existing where muscular spasm, contracture, and "epileptoid trepidation" are present, and that these conditions are associated with sclerosis of the pyramidal tracts of the spinal cord.

In the investigation of afferent nerves in tendons and such as would form the first part of a reflex loop, Tschiriew§ is generally supposed to be the first observer who discovered nerve fibres, without myeline, which terminate in the aponeuroses in the neighbourhood of tendons, which he looked on as the organs of transmission of the muscular sense. These centripetal nerves had, however, previously been noticed, but imperfectly described, by Sachs. And Golgi‖ and his pupil Cattaneo¶ fully described the nerve endings in tendons; and, although Golgi's completed work did not appear until 1880, his first publication on the subject was three years prior to this.

Nothnagel** found that when clonus existed it could be arrested instantly by pressure on the anterior crural or sciatic nerve, and that pressure on the former nerve stopped the movements in the territory of the sciatic as well as in its own, and that pressure on the nerves of one side puts an end to the phenomenon on the opposite side. Lewinski†† further showed that in cases of contracture with exalted reflexes increase of the tendon of the tension of the contracted muscle, however brought about, would evoke clonus, as would excitation of the nerve supplying the muscle with a moderate induced current; while cutaneous stimulation by pinching the skin, or by squeezing the toes or fingers, would arrest it, as would excitation of the nerve supplying the muscle with a strong induced current. If the tendon was first rendered lax, none of the methods which formerly evoked the clonus would do so.

* 'Arch. f. Psych.,' vol. 8, p. 514.

† "Des Réflexes tendineux," 'Thèses de Paris,' 1880.

‡ 'Lancet,' July, 1878.

§ 'Arch. d. Physiol.,' Series II, vol. 6, p. 89, 1879.

‖ 'Rendiconti del Reale Istituto Lombardo,' fasc. IX, p. 445; 'Gaz. Lomb.,' vol. 7, s. V, p. 23; 'Atti d. Soc. Ital. di Scienz. Nat. a Milano,' vol. 21, p. 464; and 'Memorie della R. Accad. d. Scienz. d. Torino,' vol. 32, 1880, 28 Stu., 2 Tafeln.

¶ 'Arch. Ital. de Biol.,' vol. 10, fasc. III, p. 337

** 'Arch. f. Psych.,' vol. 6, p. 332, 1876.

†† *Ibid.*, vol. 7, p. 327, 1877.

Burckhardt,* in attempting to prove that the phenomenon is a reflex, measured the time which elapsed between the percussion of the tendon and the resulting muscular contraction. His investigations led him to the conclusion that it is a reflex which is produced in the spinal ganglia and not in the cord. Following him, numerous investigators endeavoured to determine the time which elapses between the stroke and the contraction.

Brissaud,† with Franck, measured the time very exactly in healthy persons, and also in those the subjects of disease. These observers found that 0·05 second elapses in healthy subjects, but that it varies from time to time in the same individual, and is modified by conditions which alter the excito-motor properties of the spinal cord. When the lateral columns of the cord are sclerosed the time is diminished; it is the same on the two sides in a healthy subject, but is less on that side when one lateral column is more sclerosed than its fellow.

Déjerine's‡ observations and Ter-Meulen's§ researches furnished very similar results.

Gowers,‖ who registered the movement of the limb in his observations, concluded that 0·09 to 0·015 second is the time which elapses between the stroke on the tendon and the resulting movement of the limb, which time is sufficient to allow a reflex to occur. Percussion of the tibialis anticus gave a response in 0·03 to 0·04 second, which is not sufficient for a cord reflex. He therefore concluded that ankle clonus is a phenomenon of direct excitation, while the knee jerk is to be looked on as a reflex.

Waller¶ found that the time which elapsed between percussion of the tendo Achillis and contraction of the gastrocnemius was 0·3 to 0·4 second, and in the case of the quadriceps extensor and its tendon 0·3 to 0·4 second. While admitting the necessity of the integrity of the spinal cord for its production, he did not admit its reflex nature, as the time was too short for a reflex to occur. He looked on the phenomena as merely peripheral reactions, and only tests of spinal conditions in the sense that other peripheral reactions of muscles (electrical or mechanical) are tests of these conditions.

Since then new facts with regard to the knee jerk have been recorded by several observers.

* "Ueber Sehnen-Reflexe," 'Festsch. V. Haller,' Bern, 1877.

† 'Recherches Anatomo-path. et Physiol. sur la Contracture perm. des Hémipl.,' Paris, 1880.

‡ 'Comptes Rendus,' May, 1878.

§ 'Ueber Reflexprikkenbaarhied en Pessreflexen,' Amsterdam, 1879.

‖ 'Lancet,' Part I, p. 156, 1879.

¶ 'Brain,' Part X, 1880.

Hughlings-Jackson* has recorded an instance of exaggeration of the knee jerk on one side after convulsions which affected chiefly the leg on that side. This observer has also published a case in which the knee jerks, absent in a case in which the posterior columns of the cord were sclerosed, returned when the lateral pyramidal tracts became sclerosed consequent on a cerebral hæmorrhage. Dr. Jackson has also observed that the knee jerks are absent in conditions attended by hyper-venosity of the blood in man.

Beevor† found that after generalised convulsions in man the knee jerks were absent or exaggerated according as the convulsions were very severe or less so, and the former condition he ascribed to exhaustion of the lumbar centres consequent on their severe discharge of energy.

Jendrassik‡ has furnished us with a valuable method of eliciting the knee jerk when it appears to be absent in healthy persons. It consists in making the person clench the hands or perform some other violent movement at the moment when the patella tendon is struck, when the resulting jerk is found to be increased. He concluded that the knee jerk is a true reflex caused by mechanical irritation of the nerves in the tendon; that passive tension of the muscle is necessary for its production; that voluntary innervation of the crural nerve lessens or prevents it; and that innervation of the sciatic favours it.

Weir Mitchell, and Lewis,§ from a large number of investigations in man, supplemented by a few in dogs and rabbits, concluded that the knee jerk varies in health, may be exhausted by too much use, and may increase from frequent excitation. All volitional acts may increase it; and weak innervation of the crural nerve increases it, as does any form of innervation of the sciatic, while strong prohibits it. Continual violent muscular actions, as of both arms and hands, eventually enfeeble the knee jerk. Passive tension is not essential for its production, moderate tension mechanically favours it, and extreme tension destroys it even in spastic cases. An act of will directed to a part functionally inert, or to amputated parts, reinforces the knee jerk. Strong or weak stimulation of one sciatic in etherised animals intensifies the knee jerk of the other leg; and pressure on the sciatic in man sufficient to cause pain and numbness diminishes the knee jerk on that side. One knee jerk does not reinforce the other. Touch has no effect on it, but all abrupt impressions such as pain, heat, and cold anywhere on the skin increase it, as does a

* 'Med. Times and Gaz.,' February, 1881; 'Brit. Med. Journ.,' July, 1891; February and March, 1892.

† 'Brain,' Part XVII, 1883.

‡ 'Deutsches Arch. f. klin. Med.,' vol. 33, p. 177, 1883.

§ 'The Medical News of Philadelphia,' February 13th and 20th, 1886.

violent optical impression. Nitrite of amyl has no effect on the jerk, but ether abolishes it in dogs, but has a smaller effect in rabbits. Faradic currents strong enough to produce contraction of muscles increase the knee jerk, and stimulation of the dry skin has a like effect. Short voltaic currents not strong enough to cause muscles to contract are attended by the same result, as are voltaic currents applied to the head, especially the temporal regions and especially when the negative pole is applied. Making is more effectual than breaking the current, and the effects soon wear away. Long ascending galvanic currents to the spine cause marked increase, while descending cause far less, and moderate currents do not reinforce the knee jerk. These results led these observers to conclude that the knee jerk is a direct muscular act, but that it cannot exist without that spinal contribution known as tone, which is capable of increase by a variety of causes. They consider that it cannot be a reflex, as the latter are inhibited by violent sensory stimulations, which they have shown increase the knee jerk. An exactly opposite view is that taken by Lombard,* who observed that the flexors, *i.e.*, the hamstrings, sometimes contracted when the ligamentum patellæ was struck. He concluded that the flexors were caused to contract by reflex excitation, and that the whole phenomenon was of the same nature.

Bowditch and Warren† found that when a voluntary action was employed to produce exaltation of the knee jerk the reinforcement wholly depended on the interval between starting of the action and the incidence of the blow to elicit the jerk. When this was prolonged, instead of being exalted, the knee jerk became much reduced; the interval at which the effect changes from positive to negative varied from 0·22 to 0·6 second. The effect of sudden auditory or visual stimulus was usually positive. Tactile stimulation of the conjunctiva and of the nasal mucous membrane also showed the same effect.

Bastian‡ has recently brought forward striking evidence to prove that in man total transverse lesion of the spinal cord above the lumbar enlargement abolishes, instead of augmenting, the knee jerks, as is commonly supposed; and Bowlby§ has supported this view by the results of his observations in fracture of the spine with crushing of the cord.

Buzzard‖ has met with absence of the knee jerk in man when ther was extravasation of blood into the cranial cavity.

* 'Journ. of Physiol.,' vol. 10, p. 122; 'American Journal of Psychology,' vol. 1, p. 50, 1887.

† 'Journ. of Physiol.,' vol. 11, p. 25, 1890.

‡ 'Med. Chir. Trans.,' vol. 73, 1890; 'Lancet,' March, 1890.

§ 'Med. Chir. Trans.,' vol. 73, 1890; 'Lancet,' May, 1890.

‖ 'Med. Press and Circ.,' March, 1890.

History of Previous Experimental Work.

Experimental work directly bearing on the subject commenced with Schultz and Fürbringer,* who noted absence of the knee jerk after section of the crural nerve or lumbar roots in rabbits. A like result followed the administration of curara. They also showed that by striking the tendon on one side, under certain circumstances, not only that knee jerk could be elicited, but also that on the opposite side. The conclusions come to were that it is not the result of direct irritation of the muscle or its tendon, but a reflex act, the centre for which is situated in the lower part of the cord, and that there can be no question of its being in any sense a cutaneous reflex.

Tschiriew† excited the divided crural nerve electrically in order to give the muscle tonicity, but never succeeded in obtaining the knee jerk after it had disappeared on section of the nerve.

Burckhardt,‡ experimenting on rabbits, concluded that the duration of the phenomenon is less than the time necessary for a cutaneous reflex, that it subsists after section of the posterior roots of the spinal nerves and after destruction of the cord, but that it is abolished by section of the crural nerve ; hence his belief that it is a reflex produced in the spinal ganglia and not in the cord.

Tschiriew,§ with the knowledge that the crural nerve in the rabbit is formed by the 5th and 6th lumbar roots, divided the cord at the level of the 3rd lumbar, and found that the knee jerk became exaggerated, while when the section was made between the 5th and 6th roots the knee jerk disappeared. On making successive sections from the sacral region upwards he found that the knee jerk remained intact until the level of the 6th lumbar pair was reached. He divided the posterior roots of the 6th lumbar pair, taking great care not to injure the neighbouring parts, and found that such section abolished the knee jerk. Destruction of the segment between the 5th and 6th lumbar pairs resulted in abolition of the knee jerk also.

Prevost,‖ in his first series of experiments, divided the cord in the dorso-lumbar region, whereupon the reflexes below this point became exaggerated. Section of the crural nerve abolished the knee jerk, as did section of the posterior root of the 6th lumbar in the rabbit, while it was augmented when the sciatic alone was divided. These experiments, therefore, confirmed the results of previous observers, especially those of Tschiriew. The next series of experiments were

* ' Centralbl. f. d. Med. Wiss.,' p. 929, 1875.
† ' Arch. f. Psych. und Nerv. Krank.,' vol. 8, p. 694.
‡ *Loc. cit.*
§ ' Arch. de Physiol.,' Series II, vol. 6, p. 293, 1879.
‖ ' Rev. Méd. de la Suisse Romande,' February, 1881.

entirely original on the part of Prevost, and deserve careful notice. He found that in the cat deep chloroform narcosis, and the administration of curara, each individually caused abolition of the knee jerk, while profound ether narcosis, almost up to the point of cessation of respiration, failed to do so. In the rabbit, on the other hand, profound ether narcosis abolished the knee jerk. Intravenous injection of 1 gramme of chloral in 10 grammes of water, injected in small quantities into a cat until the animal was profoundly insensible, failed to have any effect on the knee jerk. 3 grammes of water containing 0·075 gramme of the hydrochlorate of morphia, injected into a rabbit in the same way, caused exaggeration of the knee jerk, the animal being in a state of torpor with diminished respiration. The third series of experiments were also original, and consisted in compressing the abdominal aorta, and thus producing anæmia of the cord, and observing the effect of this on the knee jerk. Such compression, whether employed through the integument or applied directly to the abdominal aorta, in the rabbit caused in a few seconds exaggeration, and then abolition of the knee jerk in about 45 seconds, as a rule, and it remained absent for from 15 or 20 seconds to one or several minutes, after the compression was left off, before returning. The length of time that it remained absent was found to be directly proportional to the length of time that the compression on the aorta had been kept up; the longer the compression, the slower was the knee jerk in returning. The results obtained from the various methods of experimentation led Prevost to believe that the knee jerk has a decidedly central origin, and is of the nature of a reflex, also that it is the excitation of the tendon, and not of the skin, which elicits it. He further believed that the contraction of the opposite quadriceps when the tendon of one side is struck pointed to the existence of a crossed reflex.

Waller and Prevost* soon after performed some experiments in conjunction, which proved this last conjecture to be erroneous. They divided the sciatic, anterior, crural, and posterior roots on one side, and yet did not abolish the crossed movement. Percussion of the tendon on the injured side caused no contraction on that side, but evoked a contraction on the opposite side at least as vigorous as before the injury. From this they concluded that there was no physiological transmission, and therefore no "crossed reflex," but that the result was due to physical diffusion of vibrations.

Senator† found that the hemisection of the spinal cord affected the knee jerk on the same side only; that section or greater disturbance of the posterior columns of the lumbar cord, or of the posterior horns had no effect on the jerk; and that dividing the lateral

* 'Rev. Méd. de la Suisse Romande,' June, 1881.

† 'Arch. f. Anat. u. Physiol.,' Physiol. Abth., 1880, Heft 3.

column at the level of the 5th to the 6th lumbar vertebræ augmented the jerk on that side.

The latest experimental work on the subject is that by Sherrington,* who found that section of those branches of the anterior crural which supplied the vastus internus and adjoining part of the crureus abolished the knee jerk, while when these branches were left intact, and all the other branches of the nerve divided, the knee jerk remained active. He also noted that section of the 6th roots in rabbits did not always abolish the knee jerk, but occasionally section of the 5th root alone sufficed to bring about this result. In the cat, this observer found that when all the anterior and posterior nerve roots of the lumbo-sacral region, with the exception of the 6th, were divided, the knee jerk became brisk; but that section of the 6th root instantly abolished the jerk. When only half the filaments which composed the posterior root of the 6th root were alone divided the knee jerk was at once extinguished. Section of the anterior root of the 6th root greatly diminished, but did not absolutely abolish, the jerk; when, however, the ventral root of the fifth was subsequently divided in the same animal the knee jerk was abolished. In *Macacus rhesus* division of the 5th root never failed to abolish the knee jerk, while section of all other adjacent roots only tended to render it more brisk. Section of the whole, or even half, of the posterior root of the 5th abolished the knee jerk; but when the efferent root of the 5th was divided a remnant of the jerk persisted, as long as the efferent root of the 4th lumbar was left intact. Bisection of the cord in the lumbo-sacral region of *Macacus rhesus* produced no alteration in the knee jerk. Transverse section of the cord at the level of the 9th thoracic root caused the knee jerk to disappear ten minutes later, and it did not commence to return until three weeks after. A similar lesion of the cord at the level of the 1st lumbar root, with partial section at the 3rd lumbar, caused abolition of the jerk, and it did not return during the six months that the animal was under observation. When the knee jerk was abolished by the inhalation of chloroform it did not return so rapidly when the cord had been previously divided transversely as when it was left intact.

In a later paper† Sherrington has greatly added to our knowledge of the nerve arc on which depends the efficiency of the jerk. After showing how very readily the afferent fibres in the 5th lumbar posterior root (*Rhesus*), and on which the existence of the knee jerk depends, can be impaired, he proceeded to expand the observation of Tschiriew concerning the hamstring nerve, and he then found that excitation of this branch only of the sciatic trunk inhibited the jerk (thus excluding for the most part skin paths), and further that

* 'Journ. of Physiol.,' vol. 13, No. 6, 1892.

† 'Roy. Soc. Proc.,' February 9, 1893.

stretching (moderately and gently) a hamstring muscle would produce the same effect, thus proving that afferent impulses from the hamstrings normally inhibit the jerk.

The General Plan of Research.

In the present research various circumstances under which the knee jerk is altered are dealt with, and may, for convenience of description, be best arranged in two large groups.

A. Those circumstances under which the alteration in the state of the knee jerk is brought about by some influence locally exerted on the lumbar centres.

B. Those circumstances under which the alteration is due to some remote cause. In the first of these groups are included :—

I. The effects of asphyxia.
II. The effects of the inhalation of certain gases (nitrogen, nitrous oxide, and oxygen).
III. The action of anæsthetics (ether and chloroform).
IV. The effect of anæmia of the spinal centres as brought about by compression of the abdominal aorta, or by general loss of blood.
V. The action of intravenous injections of absinthe and strychnia respectively.
VI. The result of bisection of the spinal cord made vertically at the level of the centres in which the knee jerk appears to be represented.

The second group includes :—

I. The effect of removal of a cerebral hemisphere.
II. The immediate and late effects of extirpation of different parts of the cerebellum.

And as control experiments in this connexion.

1. The effects of extirpation of the labyrinth.
2. The effects of intracranial section of the 8th nerve.
3. The effects by chemical excitation of the 8th nerve.

In every instance those circumstances under which the knee jerk is exaggerated, and those under which it is abolished, are considered ; but, inasmuch as both conditions may be brought about during different stages of the same influence, both of these states of the knee jerk are considered together.

Operative Procedure.

The anæsthetic employed to render the animal unconscious was invariably ether, except in those instances in which the effect of the action of chloroform on the lumbar centres was under consideration, when that anæsthetic was alone made use of throughout the experiment.

In every instance tracheotomy was performed, and narcosis kept up by allowing the animal to inhale the anæsthetic through the tracheotomy tube. When the effects of the inhalation of certain gases were under observation the tracheotomy tube was connected with a T-shaped glass tube by means of a short piece of india-rubber tubing; and india-rubber tubing was connected with the other two limbs of the T-tube, by which means it was easy to so arrange that the animal should inhale the particular gas from its reservoir, and exhale into the air of the room, the one tube being connected with the reservoir, and the other left free.

In those instances in which the heart beats were recorded the right carotid was exposed, opened, and a cannula inserted into it, which in turn was in connexion with a mercurial manometer. When a graphic record of the respiratory excursions was obtained it was made by means of a bertambour, whose elastic membranes were attached to a strip of Leslie's strapping which encircled the thorax. From this tambour an india-rubber tube led to a Marey recording tambour by which the respiratory excursions were registered on the cylinder.

In studying the effects of anæmia of the cord, the abdominal aorta was compressed, either by means of the thumb through the integuments, or directly after it had been exposed by dissection. General blood letting was effected by exposing and dividing one or both carotids.

Intravenous injections were made by injection with a hypodermic syringe into either a jugular or femoral vein, the minute opening made by the needle being closed by a small clip.

Bisection of the spinal cord was effected by exposing the cord at the level of the roots concerned with the knee jerk, inasmuch as division of it abolishes the phenomenon, and by means of a delicate thin-bladed knife, making a vertical incision along the middle line of the cord to the extent of two inches, with the root at its midpoint, and extending through to the anterior surface of the cord. In removing a cerebral hemisphere, a small disc of bone was first removed from one side of the cranium by means of a half-inch trephine, and then the opening was enlarged by bone forceps until the whole hemisphere was exposed. The dura mater was then dissected off, and the hemisphere removed *en masse*, or taken away piecemeal by means of a sharp scoop.

In the case of the cerebellum, a skin incision was made along the middle line down the back of the neck, and at its upper extremity a horizontal incision was carried across the vertex. The tissues were then scraped and cut away, until the occipital bone and arch of the atlas with the intervening occipito-atloid membrane were exposed; care being taken to work from the middle line outwards, as by this means hæmorrhage was found to be much less troublesome. When the superior vermis, or part of it, was to be removed, the bone covering this region was removed by means of bone forceps, and then the portion of the vermis desired excised by means of the knife. But when one or other lateral lobe was to be removed the occipital bone on that side was trephined by a half-inch trephine, and the opening increased by means of bone forceps. The dura was next dissected off, and then by means of a sharp scoop the lobe was scraped out. A syringe containing hot water (about 100° F.) was used to aid in the removal of the broken down cerebellar tissue, and in the arrest of hæmorrhage. The plan adopted in extirpating the labyrinth consisted in making a curved incision, commencing above, passing behind, and ending below the ear. The flap of skin with the pinna was then turned forward, all structures divided and scraped from the bone, so as to expose the meatus and the bone for a short distance around. The upper and posterior part of the meatus was then enlarged by means of a gouge, and by degrees the middle ear and then the labyrinth were cut into and cleared out.

When the 8th nerve was being exposed the skin incision varied little from that described above; but the bulla was more freely denuded of its soft coverings. The bulla was opened by means of a gouge, after which its inner wall was similarly cut through, until the 8th nerve was exposed. It was found that no appreciable length of the nerve could be exposed without lifting up the lateral lobe of the cerebellum, but that the nerve could be divided without interference with this structure. This plan of operation was sometimes followed in extirpating the labyrinth.

In both these methods of operating, hæmorrhage was profuse and troublesome, but was checked by the use of aseptic wax.

In those instances in which the animal was to be afterwards allowed to live the operation was conducted on strict antiseptic principles, the edges of the wound brought together by means of horse-hair sutures, and the wound dressed antiseptically.

In any instance where the operation was so severe as to lead one to suppose that the animal would be conscious of pain after the effect of the ether had passed off, a subcutaneous injection of $\frac{1}{2}$ or 1 grain of morphia was, as usual, given at the close of the operation, and repeated if necessary.

A. Circumstances under which the Alteration in the State of the Knee Jerk is brought about by some Local Action on the Lumbar Centres.

I. *The Effects of Asphyxia.*

Asphyxia was produced either by clamping a short piece of india-rubber tubing fixed to the free extremity of the tracheotomy tube, or by inserting an india-rubber plug into the tracheotomy tube directly. Before inducing asphyxia the knee jerks were carefully and repeatedly tested in order to be certain that the depth of narcosis was not such as to cause any material alteration in the state of their condition. When it was satisfactorily determined that they were as nearly as possible normal, cardiac and respiratory tracings were taken for some seconds before the tracheotomy tube was plugged. The immediate effects on the respiratory and cardiac movements do not call for description; that they were those usually met with under similar conditions is shown in fig. 1.

1. *The Effects of Asphyxia on the Lumbar Centres with the Spinal Cord Intact.*—The first effect which the altered conditions of the blood had on the knee jerk was to cause it to become exaggerated; this quickly became more and more marked, until clonus at the knee was produced by a single tap on the patella tendon; and when the exaggeration was at its maximum a tap on one tendon not only produced clonus on that side, but also evoked the knee jerk on the opposite side, even to the extent of a few clonic jerks. After this stage was reached the knee jerk became less and less marked, until it disappeared completely, and did not return up to the time of the death of the animal, when this was allowed to take place. But if, instead of allowing the animal to die, the obstruction to the entrance of air into the lungs was removed, and the animal recovered either with or without the aid of artificial respiration, the knee jerk reappeared. The time which elapsed before its reappearance depended on the length of time that the asphyxial state had been kept up; the shorter the duration of this state the quicker did the knee jerk return, and *vice versâ*. On its return the knee jerk did not at once present its normal characters; at first feeble, it quickly passed into a state of exaggeration, sometimes to the extent that a single tap on the patella tendon evoked a few clonic jerks; after a variable period this exaltation subsided, and it returned to its normal condition. The stages in the asphyxial state to which these different phenomena are related are indicated in fig. 1, which shows the respiratory and heart tracings obtained from a dog. About 2 minutes after the trachea was clamped the stage of asphyxial convulsions was reached, and after the blood pressure had risen the knee jerk

became exaggerated. This exaggeration amounted to clonus in about 30 seconds later; but about $1\frac{1}{2}$ minutes later, and after the stage of asphyxial convulsions, the knee jerk was abolished, while the blood pressure was still high, though showing signs of commencing to fall. Artificial respiration was commenced about a minute after this (see fig. 2), and $1\frac{1}{2}$ minutes afterwards the knee jerks returned, became exaggerated in about 50 seconds, and returned to their normal state about $2\frac{1}{2}$ minutes later.

The exact times at which the various phenomena occurred varied in different animals of the same class, and more widely in animals of different classes. Fig. 3 shows the approximate times at which they occurred in one of the rabbits used. In this particular instance the knee jerk became exaggerated about 50 seconds after the tracheotomy tube was plugged, and it was abolished about 70 seconds later. The plug was removed from the tracheotomy tube about 10 seconds after this, and in about 10 seconds the knee jerk returned; in about 12 seconds it became exaggerated, and returned to its normal condition after 60 seconds. In fig. 4, besides the blood and respiratory curves, a tracing of the asphyxial convulsions is shown, as obtained from the extensor muscles of the forearm of the dog, in order to show that the knee jerks were still exaggerated for some time after the convulsions had ceased.

It will thus be seen that exaltation of the knee jerk is a phenomenon of the so-called first and second stages of asphyxia, while its abolition is related to the third stage of that condition. Figs. 5 and 6 are intended to show what relationship exists between the alteration in excitability of the spinal centres and that of the cortical cells. Although the cortex exhibits some diminution in its excitability before the knee jerk is lost, yet its excitability is not completely annulled until some time after all attempts to elicit a knee jerk have failed. The preliminary exaggeration of the knee jerk commences to show itself before there is any sign of diminution of the cortical excitability.

2. *The Effects of Asphyxia on the Lumbar Centres after Total Transverse Section of the Spinal Cord in the Mid-dorsal Region.*—By this means any influence of the cerebrum and cerebellum on the phenomena was entirely excluded. It was found that, with the exception of commencing the experiment with a knee jerk more active than when the cord was not previously divided, the phenomena evoked by the asphyxial state were in every way identical to those observed before the cerebrum and cerebellum were excluded from taking any possible part in, or exerting any influence upon, their production.

II. *The Effects of the Inhalation of Certain Gases.*

1. *Nitrogen.*—As has been already noted, a ⊤-tube was made use of in these experiments; one limb of the ⊤ being connected with the tracheotomy tube, one by means of india-rubber tubing, with the gas reservoir, and one being left free with a small piece of india-rubber tubing fitted on to its extremity. The tube leading from the gas reservoir was grasped between the fingers and thumb of one hand, while the piece of tube at the extremity of the free limb of the ⊤ was grasped between the fingers and thumb of the other hand. During inspiration the free end was closed, while the tube from the bag of nitrogen was left free, and during expiration the tube from the nitrogen was closed, and that opening into the air of the room was opened. In this way nitrogen gas was alone inspired, while expiration took place into the air of the room.

Except that it took a longer time to obtain the results, the effects were identical with those met with in asphyxia.* The loss of knee jerk was preceded by the stage of exaltation, and when the animal was allowed to recover the absence of knee jerk was followed by a stage of slighter exaltation before its return to the normal state, such as existed before the administration of the nitrogen.

2. *Nitrous Oxide.*—The plan of procedure was the same in these experiments as in the last, and the results differed from them in no way. Loss of the knee jerk was always preceded by a stage of exaltation, and when the animal was allowed to recover, the normal state of the knee jerk was only reached after passing through a period during which it was exalted.

3. *Oxygen.*—Here again the plan of procedure was the same as in the experiments with nitrogen; but the results were widely different. Indeed, they were totally different from any that had been previously obtained, for in no case was the knee jerk abolished, no matter how long the so-called apnœic state was kept up. Increased activity of the knee jerk, gradually becoming more so until clonus developed, was the only effect of inhalation of this gas. When its administration was discontinued the knee jerk gradually returned to the condition in which it was before the inhalation of oxygen was commenced.

III. *The Action of Anœsthetic Agents.*

1. *Ether.*—In profound narcosis induced by the inhalation of ether the knee jerk is abolished; but this stage is preceded by one of increased activity, and followed by a similar stage of exaltation when the animal is recovering from the effects of the anæsthetic, and before the knee jerk returns to its normal conditions. The length of time

* *Cf.* Martin, 'Journ. of Physiol.'

that the knee jerk remains absent depends entirely on the depth of narcosis, and the length of time this is continued, these bearing a direct ratio to each other. The exaggeration of the knee jerk which has been alluded to is never so pronounced as in simple asphyxia or the condition induced by nitrogen or carbonic oxide; but it is nevertheless perfectly distinct.

2. *Chloroform.*—The results obtained were identical with those obtained with ether, with two important exceptions, however; thus, the knee jerk is lost very much more rapidly under its influence than under the influence of ether, and after the administration of the narcotic is discontinued a longer period elapses before the knee jerk shows any sign of returning than after a similar depth and duration of ether narcosis.

These effects with ether and chloroform were obtained both when the spinal cord was intact and when it had been previously divided transversely in the mid-dorsal region.

IV. *The effect of Anæmia of the Spinal Centres as brought about by Compression of the Abdominal Aorta or by General Blood-letting.*

1. *Compression of the Abdominal Aorta.*—This was effected by means of the thumb, either through the structures composing the abdominal wall in the rabbit, or after the artery had been exposed by dissection (rabbit and dog). The resistance offered by the bony spinal column makes it exceedingly easy to entirely stop the flow of blood in the aorta beyond the point at which compression is made by the thumb. As Prevost* found, after the compression had been kept up a short time the knee jerk disappeared, and the time that it continued absent after the compression had been taken off varied directly as the time that the compression had been maintained; the longer the compression, the longer did the knee jerk afterwards take to return. Before the knee jerk was abolished, and after it was abolished and before it returned to its normal state, it passed through stages of exaltation, as has been already observed to be the case in other conditions attended with loss of the knee jerk.

2. *General Blood-letting.*—The carotid artery was opened on one or other side, and the animal allowed to gradually bleed to death. As more and more blood was lost so the knee jerk became more and more active at first; but after a time it gradually became less so, until it eventually disappeared entirely, and did not reappear up to the time of the death of the animals.

* *Loc. cit.*

V. *The Action of Intravenous Injections of Absinthe and Strychnia.*

1. *Absinthe.*—The action of this drug on the lumbar centres was tried, both when the spinal cord was intact and after transverse section of it in the mid-dorsal region. As has been explained, a jugular or femoral vein was exposed, and varying doses of the essential oil of absinthe were injected into it, according to the class of animal under observation and the particular effect which was aimed at. Doses short of those necessary to evoke generalised convulsion were attended by increase of the knee jerk, whether the cord was intact or divided in the dorsal region. Doses sufficiently large to evoke powerful generalised convulsions were also followed by increase of the knee jerk after the convulsions ceased.*

When the spinal cord had been previously divided transversely in the dorsal region, and the lower extremities thus excluded from the otherwise general convulsions, the increase of the knee jerk, after large doses of absinthe, was still observed. The increase never amounted to clonus or tonus, but was nevertheless well marked. This effect of absinthe on the lumbar centres was strikingly demonstrated in the following experiment. The spinal cord of a dog was divided transversely in the mid-dorsal region when the animal was so profoundly under the influence of ether that the knee jerk could not be obtained. The animal was then kept lightly under the influence of the anæsthetic, but, in spite of this, the knee jerk had not returned fifteen minutes after the cord had been divided. Three minims of the essential oil of absinthe were then injected into the femoral vein of one side, and the knee jerk of the opposite side kept under observation. Well-marked convulsions occurred in a few seconds, limited to those parts above the spinal cord lesion, while the parts below the lesion remained inactive. At the time that the convulsions above the cord lesion were at their height there was doubtful evidence of return of the knee jerk. As there was absolutely no sign of the presence of the knee jerk ten minutes after the first injection of absinthe was given, 2 minims more of the essential oil were injected into the same vein. As before, convulsions occurred in those regions whose nerve supply was derived from the central nervous system above the lesion in the spinal cord, while those regions which derived their supply from below this point remained passive. A few seconds after this further administration of the drug there was undoubted return of the knee jerk, which persisted for a minute or two and then disappeared. Ten minutes after the second dose of absinthe was given a third dose of 2 minims was injected into the same vein as on the two former occasions with exactly similar results with respect to the convulsions. The knee jerk was obtained a few seconds after the

* Beevor, *loc. cit.*

absinthe had been injected, and did not again disappear in the course of half an hour, during which time it was under careful observation.

2. *Strychnia.*—The effect of this drug was only tested in the dog. Two minims of a 1 per cent. solution of strychnia were injected into the femoral vein, after the spinal cord had been previously divided transversely in the mid-dorsal region. Powerful convulsions quickly followed in all parts whose nerve supply was derived from above the cord lesion, while those whose nerve supply was from below this point remained free from convulsion. The knee jerk was increased at first slightly, but soon more so, and on injecting 1 minim more of the same solution of strychnia into the femoral vein as before, a single tap on the patella tendon was sufficient to evoke tonus in the quadriceps extensor.

When strychnia was administered without the spinal cord being previously divided, general convulsions of course resulted, and these seriously interfered with the observations on the knee jerk, as even when the animal was not in a comparatively quiescent state a tap on the quadriceps tendon usually sufficed to evoke convulsions. The plan of first dividing the spinal cord transversly in the dorsal region was therefore that usually adopted in observing the effects of strychnia on the knee jerk, and in all cases there could be no question as to the increase of the jerk under the influence of this drug.

VI. *The Results of Section of the Spinal Cord.*

1. Transverse Section.
2. Vertical Section.

1. *Transverse Section of the Spinal Cord.*—It has long been recognised that in the lower animals complete transverse section of the spinal cord above the level of the lumbar enlargement is followed by increased activity of the knee jerk. My own experiments in the dog show that the immediate effect of such a lesion depends on the depth of narcosis. The cord was always divided at or about the mid-dorsal region, and in no instance did the knee jerk disappear after such section of the cord when there had been no doubt as to its presence before the lesion was inflicted, while usually there was no difficulty in being certain of its increased activity under such circumstances. The depth of ether narcosis, however, plays a most important part in this connexion, for if the cord were divided when narcosis was so profound that the knee jerk was almost abolished, the section of the cord hastened the result; and when the cord was divided when the depth of narcosis was such that the knee jerk was abolished, the latter remained absent for a much longer time than is usual after

suspension of the administration of the anæsthetic when the spinal cord has not been divided.

2. *The Effect of Bisection of the Spinal Cord vertically at the level of the centres on whose activity the knee jerk depends.*—These experiments were undertaken to ascertain whether or no the centres to which the knee jerks are related are separate and independent in their action on the two sides, or whether the centre on one side is in any way related to its fellow of the opposite side, and depending on its co-operation for the proper performance of its functions. Since these experiments were performed Dr. Sherrington has published the results of similar experiments carried out by himself in connexion with the lumbar cord of *Macacus rhesus*. My results entirely agree with his, and showed that dividing the cord into two lateral halves, the incision commencing at the level of the 1st lumbar roots and extending to the level of the 1st sacral pair, had no appreciable effect, either in increasing or diminishing the knee jerks.

B. Circumstances under which the Alteration in the State of the Knee Jerk is due to some Remote Cause.

I. *The Effect of the Removal of a Cerebral Hemisphere.*

Either hemisphere was selected, and during the process of exposing it great care was taken to prevent the animal from losing more blood than was absolutely unavoidable. When everything was ready for the removal of the hemisphere the knee jerks were carefully tested, so as to be certain that nothing had occurred to render them unequal during the preparatory operation. The hemisphere was then excised after the dura mater was dissected off it. The effect was immediate and striking, the knee jerk on the opposite side of the body becoming distinctly more active than that on the same side as that on which the cerebral hemisphere was removed, this inequality being due to an increased activity of the knee jerk on the opposite side, and not to a diminished activity of that on the same side.

II. *The Immediate and Late Effects of Extirpation of Portions of the Cerebellum.*

1. *The Immediate Effect of Extirpation of Portions of the Cerebellum.* —*a.* The removal of one lateral lobe was followed by great exaggeration of the knee jerk on the same side, while that on the opposite side was considerably diminished. So great was the exaltation of the knee jerk on the same side as that on which the cerebellar lobe was excised, that often a single tap on the patellar tendon sufficed to produce tonic extension of the limb.

When after extirpation of one lateral lobe of the cerebellum the opposite one was also removed, the knee jerk on the side corresponding to that on which the lobe was more recently removed became increased, while there was some diminution of the knee jerk on the side on which the lobe was first removed, the two knee jerks being as nearly as possible equal, and, while both knee jerks were exaggerated, they were not as much so as was the one when only one cerebellar lobe was removed.

The depression of the knee jerk on the opposite side under these circumstances was a phenomenon less marked than was the exaltation of that on the same side as that from which the cerebellar lobe had been removed. In order to test this point further, one cerebral hemisphere was first removed, with the result that the knee jerk on the opposite side became more active than it was before.

A curious and interesting ether effect was observed in connexion with this difference of the knee jerks on the two sides when one lateral lobe of the cerebellum was removed. While the above results obtained during ordinary moderate ether narcosis, the result was exactly the reverse when anæsthesia was very profound, for then the knee jerk which was formerly exalted became depressed, even abolished, while that which was formerly lessened became markedly exaggerated.

The lateral lobe of the cerebellum on the same side as that on which the cerebral hemisphere was removed was next extirpated, when the active knee jerk on the opposite side became less so.

On account of the risk of complication by injury of other parts, no attempt was made to do more than remove the whole of the *posterior* part of the vermis of one lateral half of this posterior portion. When only the half of this posterior portion was removed, there was slight increase of the knee jerk on the same side, but this increase was in no way comparable to the great exaggeration which followed removal of one lateral lobe. As far as could be determined, the knee jerk on the opposite side was in no way altered by this lesion. When the whole of the posterior portion of the vermis was removed both knee jerks became slightly increased.

2. *The Late Effects of Extirpation of Portions of the Cerebellum.*—On the day after the operation of removal of one lateral lobe of the cerebellum the knee jerk on the same side was still exaggerated, though less so; but although the knee jerks on the two sides were still unequal, that on the opposite side was no longer feeble, but was slightly exaggerated. In the course of the second and third days it became difficult to be certain that any inequality existed on the two sides, both knee jerks being very much exaggerated, though neither of them as much so as was the one on the side of the lesion immediately after the operation. A month or six weeks after the

operation most of the animals showed a slight inequality of the knee jerks, so that, although both were exaggerated, that on the side corresponding to that from which the cerebellar lobe had been removed was slightly the more so; but in some animals the inequality was not evident. When half of the posterior part of the vermis was removed, it was usually difficult next day to say which knee jerk was the more active; but, as in the case of the lateral lobe, after a few weeks a difference on the two sides could be once more detected in most of the animals. At this time the knee jerk on the opposite side was usually as nearly as possible normal, while that on the same side as the cerebellar lesion was more active than normal. In like manner the increase of knee jerk produced by removal of the whole of the posterior portion of the vermis persisted.

If, after a one-sided lesion, either of the vermis or lateral lobes, the animal was placed under the influence of ether, the inequality of the knee jerks became more pronounced; and if the anæsthetic was pushed to the point at which abolition of the knee jerks results, that on the opposite side usually disappeared sooner than did that on the side corresponding.

There seemed, therefore, little reason to doubt that the effects obtained in connexion with the knee jerk when portions of the cerebellum were removed were directly the result of the cerebellar lesion. However, Professor Victor Horsley kindly drew my attention to the fact that the proximity of the auditory nerve and labyrinth made it necessary to institute control experiments, with a view to excluding the possibility of the effects being wholly or partly due to interference with one or other, or both, of these structures. He suggested that the labyrinth should be extirpated on one side in some animals, while in some others the 8th cranial nerve on one side could be subjected to chemical excitation. I accordingly performed the following control experiments.

III. *Extirpation of the Labyrinth on one side.* (*Control.*)

No inequality was produced in the knee jerks by this at the time of the operation, nor was any alteration detected two weeks after the operation, except in one instance, in which, two weeks after the operation, the knee jerk on the same side as the ear lesion seemed slightly more active than its fellow of the opposite side. As there was suppuration in the deep wound in this case, it was thought that the result probably depended on entrance of pus into the region of the lateral lobe of the cerebellum on the same side, but no such condition was macroscopically obvious at the autopsy, so that this case is difficult of explanation.

IV. *Intracranial Division of the 8th Nerve on one Side. (Control.)*

No inequality in the knee jerks was produced, either at the time of the operation, during the few hours immediately following the operation, or at any time during the week, after the section of the 8th nerve.

V. *Chemical Irritation of the 8th Nerve on one Side. (Control.)*

It was found impossible to expose a sufficient length of the nerve to apply an irritant to it without lifting up the lateral lobe of the cerebellum. As any interference with the cerebellum would have vitiated the experiment, it was decided that, instead of applying the irritant directly on the nerve, it should be placed in the labyrinth instead. Accordingly the labyrinth was opened, and a small portion of the 8th nerve exposed as it entered the labyrinth. Crystals of chloride of sodium were next carefully packed around the stump of the nerve and kept in position by means of a plug of aseptic wool introduced into the labyrinth. The knee jerks were carefully tested immediately after the operation, and frequently during the same day, but no alteration could be detected in them, and they remained normal and equal on the two sides during the week that they were kept under observation.

Summary and Conclusions.

I. *The Effects of Asphyxia.*

The results obtained in asphyxia appear to be due in great measure to cutting off the supply of oxygen to the lumbar centres. The preliminary exaggeration of the knee jerk might have been due to the taking off of cortical control from the lumbar centres, letting them go, so to speak, as suggested by Hughlings-Jackson,* for, as numerous experimenters have shown, asphyxia diminishes, and in an extreme degree annuls, the excitability of the motor cortex. That this hypothesis cannot be entertained is proved by the following facts. At the time when the knee jerk first becomes exaggerated the excitability of the motor cortex is little, if at all, diminished, and is not annulled until a considerable time after the knee jerk is abolished. Further, and this appears to me more conclusive evidence, the same exaggeration of the knee jerk was met with when asphyxia was induced in animals whose spinal cords were divided above the lumbar enlargement, in which case any cerebral influence was entirely put out of court. As far as the preliminary exaltation of the knee jerk is con-

* 'Brit. Med. Journ.,' February, 1892.

cerned, therefore, we must look to the spinal centres alone for explanation of the phenomenon. The rise of blood pressure which occurs in the first stage of asphyxia might be held accountable for the exaltation of the knee jerk; but that this is not the true explanation seems evident, owing to exaltation being met with in anæmia of the cord, and in the marked fall of blood pressure in general blood letting. That it is due to an irritable condition of the lumbar cells induced by depriving them of their normal supply of oxygen is rendered probable from the following facts, as well as those just mentioned.

What part, if any, the presence of excess of carbonic acid in the lumbar centres plays in the production of the phenomenon, it is difficult to estimate. That the absence of oxygen is alone capable of producing it is shown by the effects of anæmia of the cord, and by the fact that when nitrogen gas is inhaled the same result is obtained; for in this latter instance most of the oxygen in the body is used up, and the nitrogen takes its place, but there is not necessarily any excess of carbonic acid, since there is no obstruction of expired air, merely the entrance of nitrogen instead of oxygen being provided for. One thing is, however, evident, viz., that in all these conditions the effect is not so rapid as in asphyxia; therefore it is not improbable that the presence of excess of carbonic acid hastens the results.

The abolition of the knee jerk might be due to exhaustion of the lumbar centres by the asphyxial convulsions, for Beevor* has shown that after severe epileptic convulsions in man the knee jerk may be abolished, and this has been attributed to exhaustion of the lumbar centres, consequent on their great discharge of energy. That this is not the explanation of the phenomenon in asphyxia is proved by the fact that it occurs when the spinal cord has been divided transversely in the dorsal region prior to the occurrence of asphyxial convulsions, and where, therefore, the lumbar cells are not discharged during the asphyxial spasms, and consequently cannot be exhausted in this way. Indeed it appears not improbable that the effects in man which have been attributed to exhaustion of the lumbar centres may after all be due to the asphyxiated condition of the blood, which occurs in a severe epileptic seizure, consequent on the arrest of respiration due to the tonic spasm of the muscles of respiration.

That the failure of the knee jerk is consequent on the fall of blood pressure which takes place in the third stage of asphyxia seems improbable, as the knee jerk is lost just when the blood pressure commences to fall, often, indeed, before there is any distinct evidence of the decline of blood pressure. Then also in general loss of blood the blood pressure falls very considerably lower than the height at which it stands when the knee jerk is lost in asphyxia without any sign of loss of knee jerk, which does not take place till much later.

* *Loc. cit.*

I trust, therefore, we are justified in concluding that the failure of the spinal centres, to which the knee jerk is related, to perform their functions is due in large measure to their being starved of oxygen; for this same starvation occurs in asphyxia when nitrogen or nitrous oxide is inhaled, and when anæmia of the lumbar cord is produced; in all these conditions abolition of the knee jerk being the ultimate result observed.

With regard to the part played by carbonic acid in helping to bring about this effect, what has already been said with reference to the preliminary exaltation of the knee jerk is wholly applicable; therefore nothing further need be said on this subject.

The behaviour of the knee jerk when it reappears after being absent for a time, taken in connexion with its behaviour when first deprived of its normal supply of oxygen, and before it was abolished, suggests the probability that not merely the presence of oxygen is necessary for the lumbar cells to functionate normally, but a certain definite quantity of that gas. And this normal balance appears to be upset either by an insufficient quantity of the gas, or by too much of it; for when pure oxygen is inhaled the same exaltation is observed.

II. *The Effects of the Inhalation of certain Gases.*

The results obtained with nitrogen and nitrous oxide, coinciding as they do with those obtained in asphyxia, lend strength to the hypothesis which has been advanced in explanation of the phenomena related to asphyxia; for when either of these gases is inhaled, to the entire exclusion of all atmospheric air, the blood is principally deprived of its oxygen, and so also the lumbar centres. Here, again, it is therefore probable that the absence of oxygen is to be looked on as the prime factor which brings about the alterations in the knee jerk, which have been already detailed, the exact form of alteration apparently depending on the amount of oxygen left in the blood. When the amount of oxygen in the blood is small, or only moderate, the lumbar centres become more excitable, while when it is absent, or only present in very minute traces, inaction of these centres results.

III. *The Effects of Ether and Chloroform.*

That the results obtained with these drugs are due to their direct action on the lumbar centres is shown by the fact that the results are almost identical, whether these centres have or have not been cut off from their connexion with higher centres by complete transverse section of the cord in the dorsal region. It is a little curious that the lumbar centres should show the same increased excitability when

these poisons have acted on them for a certain time, just as when they have been deprived of a certain amount of their supply of oxygen. That they should fail to act after they have been subjected to the influence of such powerful poisons is not surprising. It may, of course, be urged that the results obtained with these drugs are not the result of their specific action on the lumbar centres, but of the want of oxygen. While it cannot be denied that this may play some part in the production of the phenomena, that the direct action of the poisons is mainly responsible there can be little doubt, for during the respiration of these vapours, in the manner employed in their administration to animals, the entrance of atmospheric air is not excluded, so that, while possibly the interference with the supply of oxygen to the lumbar centres might account for the preliminary exaltation of the knee jerk, it can never be nearly so great as to bring about the abolition of the knee jerk, which, as has been shown, takes a considerable time to disappear, even after the fresh supply of oxygen to the blood has been completely cut off. Further, and this is more convincing, the effects of chloroform and ether respectively differ in two important respects, since (1) the effects on the knee jerk are brought about very much more rapidly when chloroform is inhaled than when ether is administered, and (2) the effect produced by chloroform continues longer after its administration is discontinued than does the same effect when produced by ether. Nothing but certain inherent properties of these drugs can be reasonably believed to be the causes of these differences, for, if venosity of blood was alone or mainly responsible for the results, the effects produced by ether should be more rapid and powerful than those produced by chloroform, since greater venosity is observable in the case of the former than the latter drug. It seems not unreasonable to assert, therefore, that the results obtained with ether and chloroform are mainly due to the direct action of these drugs on the lumbar centres.

IV. *The Effect of Anæmia of the Spinal Centres.*

Deprivation of the lumbar cord of its blood supply, either by direct pressure on the abdominal aorta or by general blood letting, is synonymous with depriving it of its normal supply of oxygen. But another factor has to be taken into consideration in this relation, for both of these methods of experimentation are attended with notable lowering of the blood pressure in the lumbar cord. That the shock occasioned by such lowering of blood pressure, whether resulting from the more or less sudden effect of clamping the aorta, or the more gradual lowering in general loss of blood, is capable of causing abolition of the knee jerk is not improbable; but that this is the true explanation of the occurrence of the phenomena is made improbable,

when it is remembered that exaltation of the knee jerk precedes its disappearance, for in no known method of producing shock of the spinal cord is there an increased excitability of its centres before their failure to act. It seems, therefore, more feasible to attribute the whole of the result, as far as exaltation of the knee jerk is concerned, to the absence of oxygen.

V. *The Action of Intravenous Injections of Absinthe and Strychnia.*

On the supposition that the former of these drugs acts mainly on the cerebral cortex, and possibly in some degree on the bulbar centres, but little, if at all, on the lower spinal centres, this drug was given in doses sufficiently large to produce powerful generalised convulsions, in order to test whether or no there is any evidence of exhaustion of the lumbar centres after such discharges, when the paths from these centres to the cerebrum, and from the cerebrum to them, are left intact. It was found that, in spite of the most powerful and oft-repeated generalised convulsions, there was increased action rather than depression of the lumbar centres, as evinced by increase of the knee jerk. That this was not a fair test of the condition of the lumbar centres, as comparable to their condition when generalised convulsions result from some condition which evokes discharge from the higher centres alone, is proved by the results obtained with absinthe, when the lumbar cord had been severed from its connexion with the higher centres by complete transverse section of the cord in the dorsal region. When this was done it was found that, though no convulsions in those parts enervated from the spinal cord below the level of the transverse lesion, yet there was abundant evidence of a considerable direct action on the spinal centres, as proved by the re-establishment of the knee jerk when its absence probably depended on shock to the lumbar centres, and of its increased action when it was comparatively normal before the administration of the drug. That strychnia should cause increase of the knee jerk, whether the spinal cord was intact or divided transversely in the dorsal region, was only what was expected from the well-known powerful action of the drug on the spinal cord. It is thus clear that absinthe, like strychnia, has a direct action on the lumbar centres, but that this action is very much less pronounced in the case of the former than in that of the latter drug.

VI. *The Results of Section of the Spinal Cord.*

That complete transverse section of the spinal cord, sufficiently high up not to interfere with the lumbar centres either by direct mutilation, shock, or myelitic softening consequent on the lesion, does not

abolish the lesion in the lower animals, but, on the contrary, causes distinct increased activity of it, is a well-established fact, which did not require the further support which the results of these experiments give to it. The chief interest in the present experiments, however, is centred in the varying effect obtained according to the depth of ether narcosis; and they demonstrate very clearly how greatly shock to the spinal cord may be increased by the depth of narcosis. That is, a lesion of such severity and in such a situation as to cause very little or no shock to the lumbar cord under moderate ether narcosis may be made to produce considerable shock if the depth of narcosis be greater at the outset.

The results of bisection of the spinal cord in the lumbo-sacral region prove, in confirmation of Sherrington's observations, conclusively that the centres on whose action the knee jerk depends are distinct in the two lateral halves of the cord, and are not dependent on each other, either for control or for reinforcement.

The Effects of Removal of a Cerebral Hemisphere.—The increase of the knee jerk on the opposite side, which followed the removal of the cerebral hemisphere of one side, is a result in keeping with the best established views of the relation of the lower spinal centres to the higher cortical ones; for, by removing the hemisphere the control which the cortical centres are regarded generally as exercising over the spinal centres of the opposite side chiefly was removed.

The Immediate and Late Effects of Extirpation of portions of the Cerebellum.—As has been seen, the knee jerk on the same side became exaggerated both when one lateral lobe of the cerebellum or when one half of the posterior part of the vermis was removed, and that this increase of the knee jerk persisted for weeks, *i.e.*, after all phenomena which could be ascribed to "irritation" had passed off. It seems justifiable therefore to attribute this to a "paralytic" rather than an "irritative" lesion. This being the case, two hypotheses are open to us in explanation of the phenomenon: either we must suppose that the one half of the cerebellum exercises an energising influence on the opposite half of the cerebrum, in virtue of which it causes the opposite cerebral centres to hold in greater check the spinal centres of the side of the spinal cord corresponding to the side of the cerebellar lesion; or that the one half of the cerebellum exercises a controlling influence on the spinal centres on the same side of the spinal cord. If the first of these hypotheses is accepted, then the increase of the knee jerk is due to the diminished power of control of the cerebral centres on those in the spinal cord in consequence of the loss of the energising influence of the cerebellum on the cerebrum. If, on the other hand, the second of these hypotheses be accepted, the increase of the knee jerk is due directly to the taking off of cerebellar control from the spinal centres. That the first of these hypotheses

does not wholly meet the case is, I think, clear on two grounds. The increase of the opposite knee jerk which is consequent on the removal of the cerebral hemisphere of one side is not nearly so great as that brought about by the removal of the lateral lobe of the cerebellum of the same side. When one cerebral hemisphere has been first removed, and the opposite lateral lobe of the cerebellum is removed, the knee jerk on the opposite side from the cerebral and on the same side as the cerebellar lesion is further increased after the second operation. It thus seems clear that the cerebellum exercises an independent action on the spinal centres from that exercised by the cerebrum, and that this action is of the nature of a control over the spinal centres chiefly of the same side. That this is the chief explanation of the phenomenon there appears little doubt; but it does not entirely negative the possibility of the first hypothesis being wholly or in part true.

The fact that the diminution of the knee jerk, on the side opposite to that on which the lateral lobe of the cerebellum was removed, was always of such short duration, points to that phenomenon as being an "irritative" one, possibly one of inhibition.

The curious ether effect which was observed in this connexion is easy of explanation as far as the knee jerk of the opposite side is concerned, when it is considered alone; for, if it be admitted that the inhibitory influence of the cerebellar lesion is sufficient explanation for the occurrence of diminution of the knee jerk, it is easy to understand how the first effect of the ether would be to remove this inhibitory influence, and by its direct action on the spinal centres to cause exaggeration of the knee jerk. The effect of the ether on the knee jerk of the same side as the cerebellar lesion is also easy of explanation, when considered by itself, for the direct effect of the ether on the spinal centres, when present in sufficient quantity, would be to cause diminution, and finally abolition, of the knee jerk. When both phenomena, *i.e.*, those of the opposite sides, are considered together, the explanation becomes more difficult; for, in order that the explanations suggested when the phenomena were separately considered should hold good now that they are considered in conjunction, one of two things must be admitted: either some influence on the spinal centres of the side corresponding to that of the cerebellar lesion has rendered them less capable of resisting the direct action of the ether; or some influence acting on the spinal centres of the opposite side has rendered them more resistant to the action of that drug.

These questions must for the present remain unanswered.

That interference with the 8th nerve or labyrinth plays no part in the phenomena which follow extirpation of parts of the cerebellum is abundantly proved by the control experiments which were performed in order to decide this question.

FIG. 1.

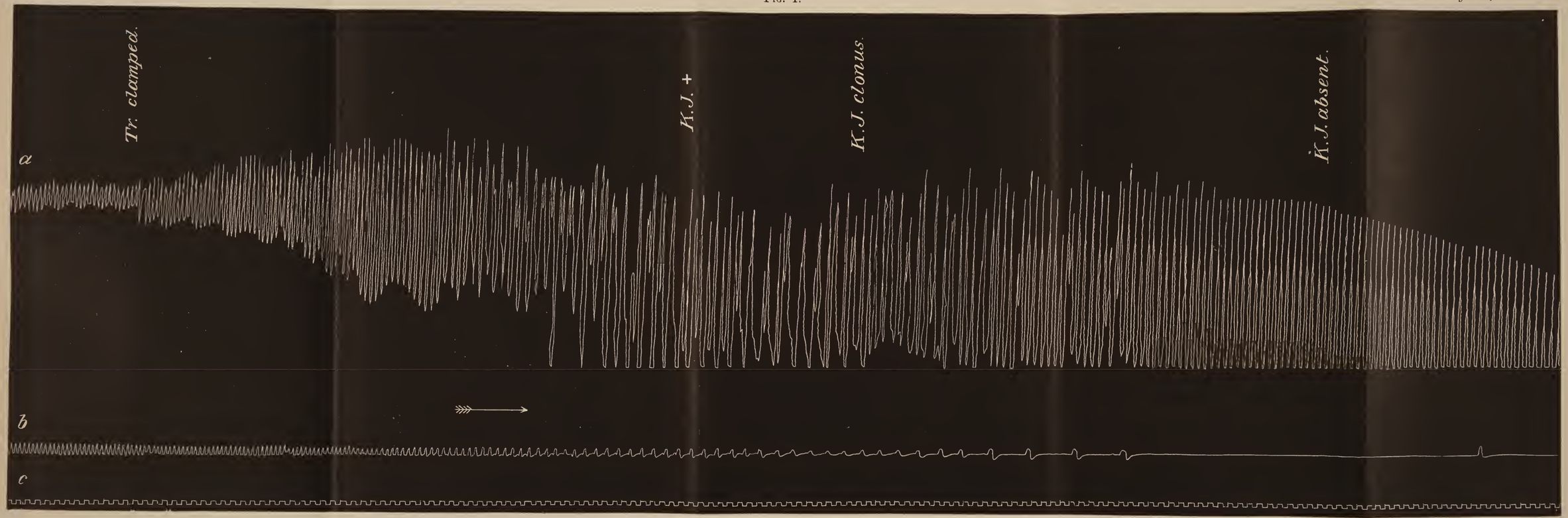


FIG. 2.

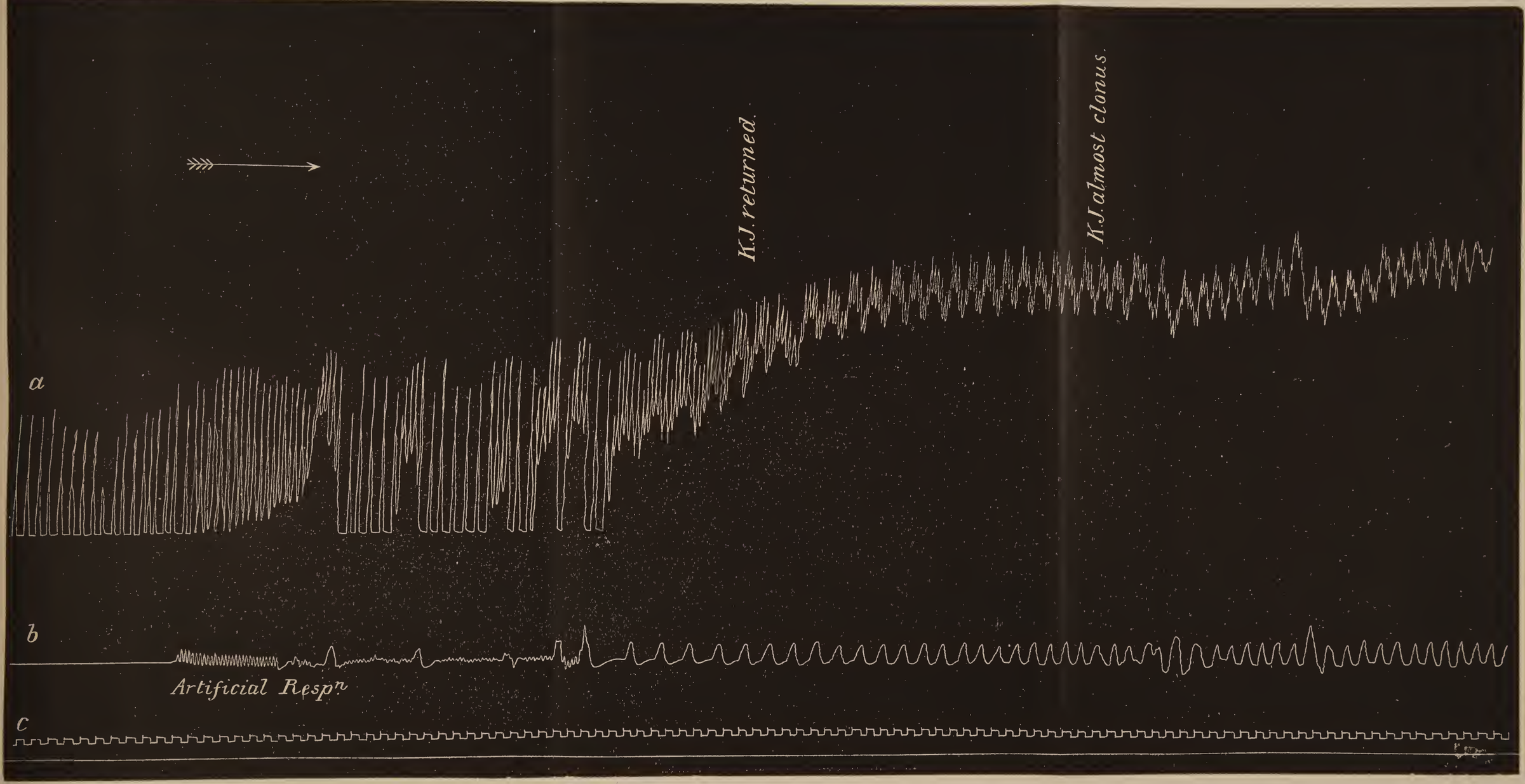


FIG. 3.

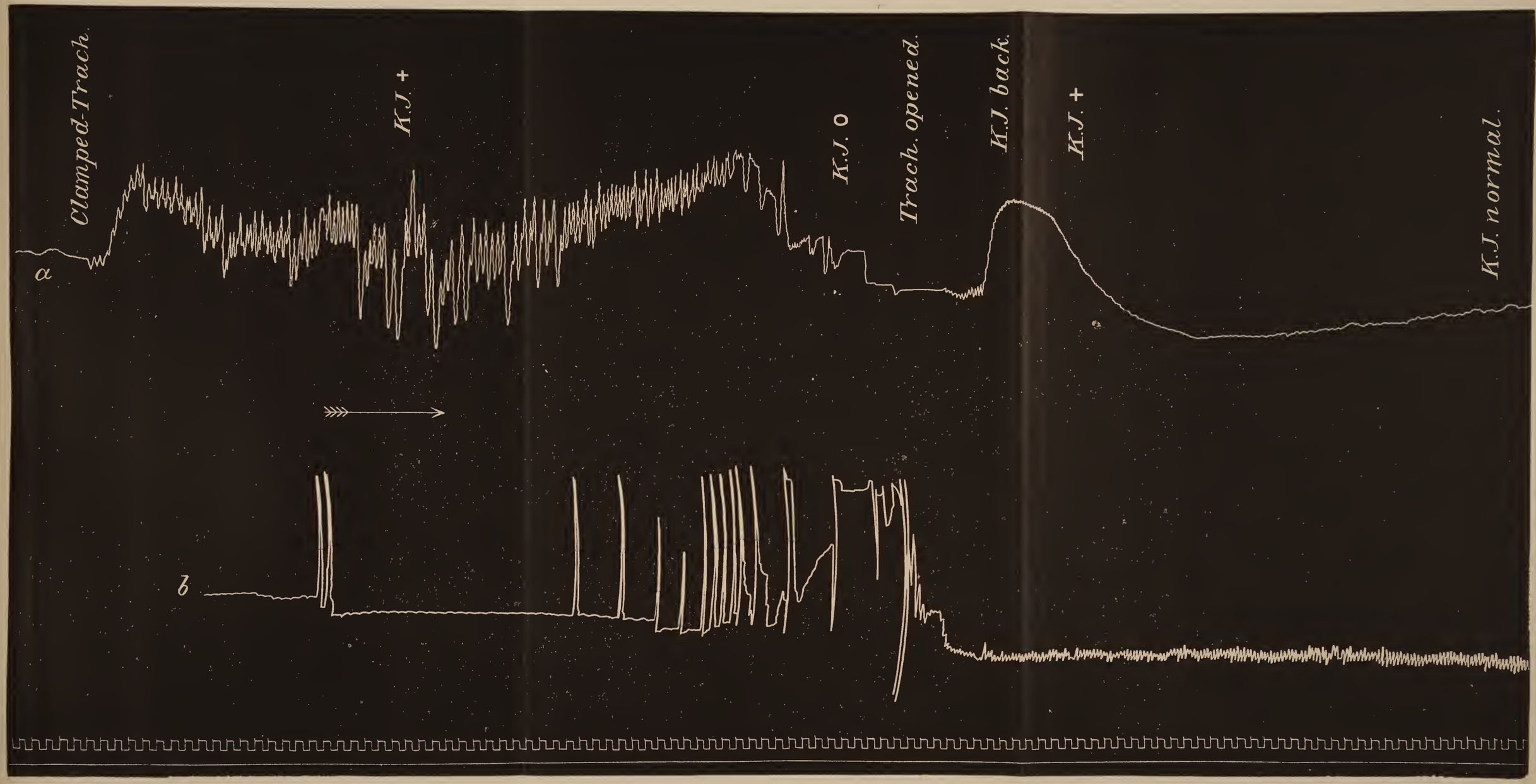


FIG. 4.

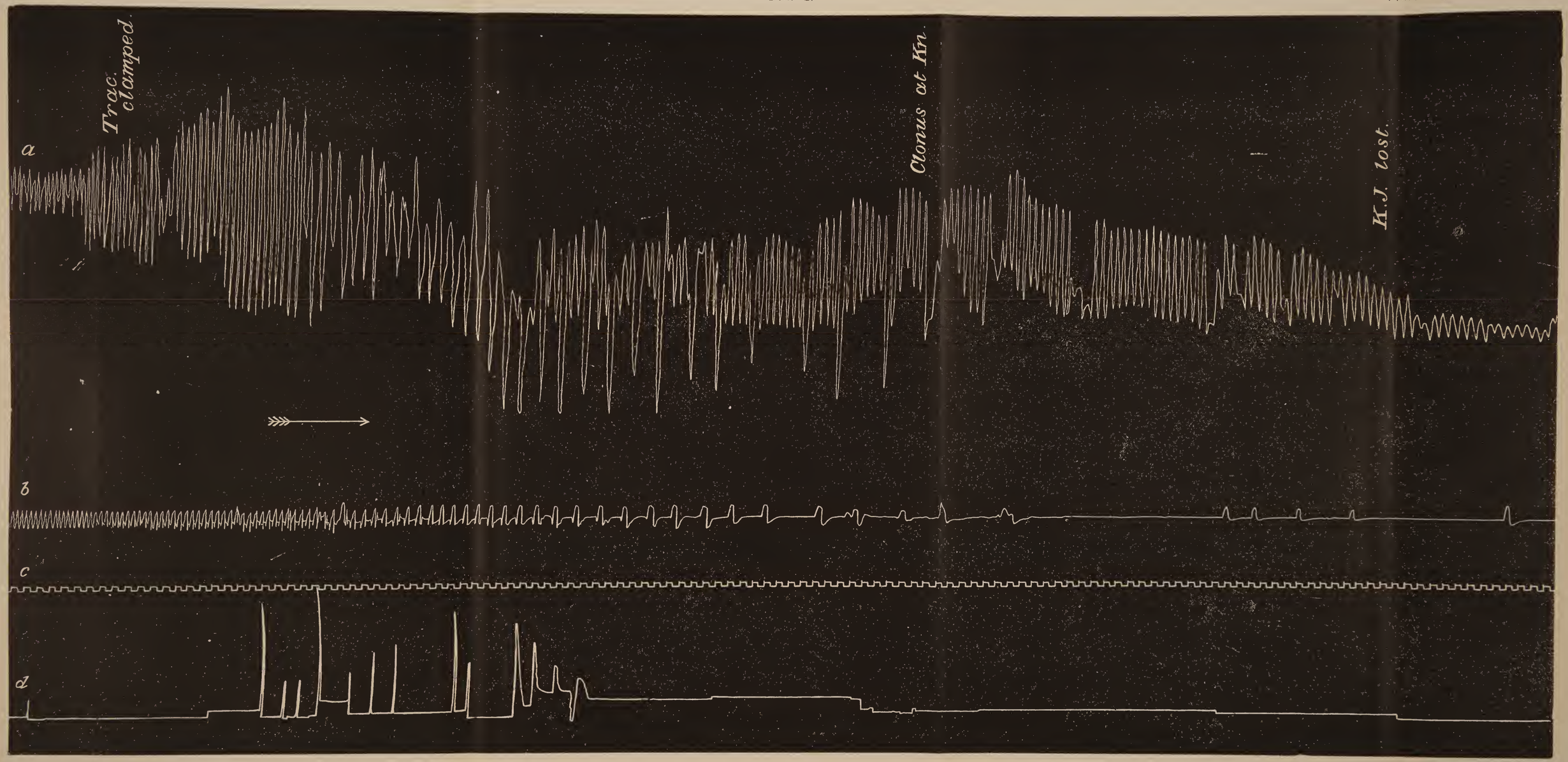
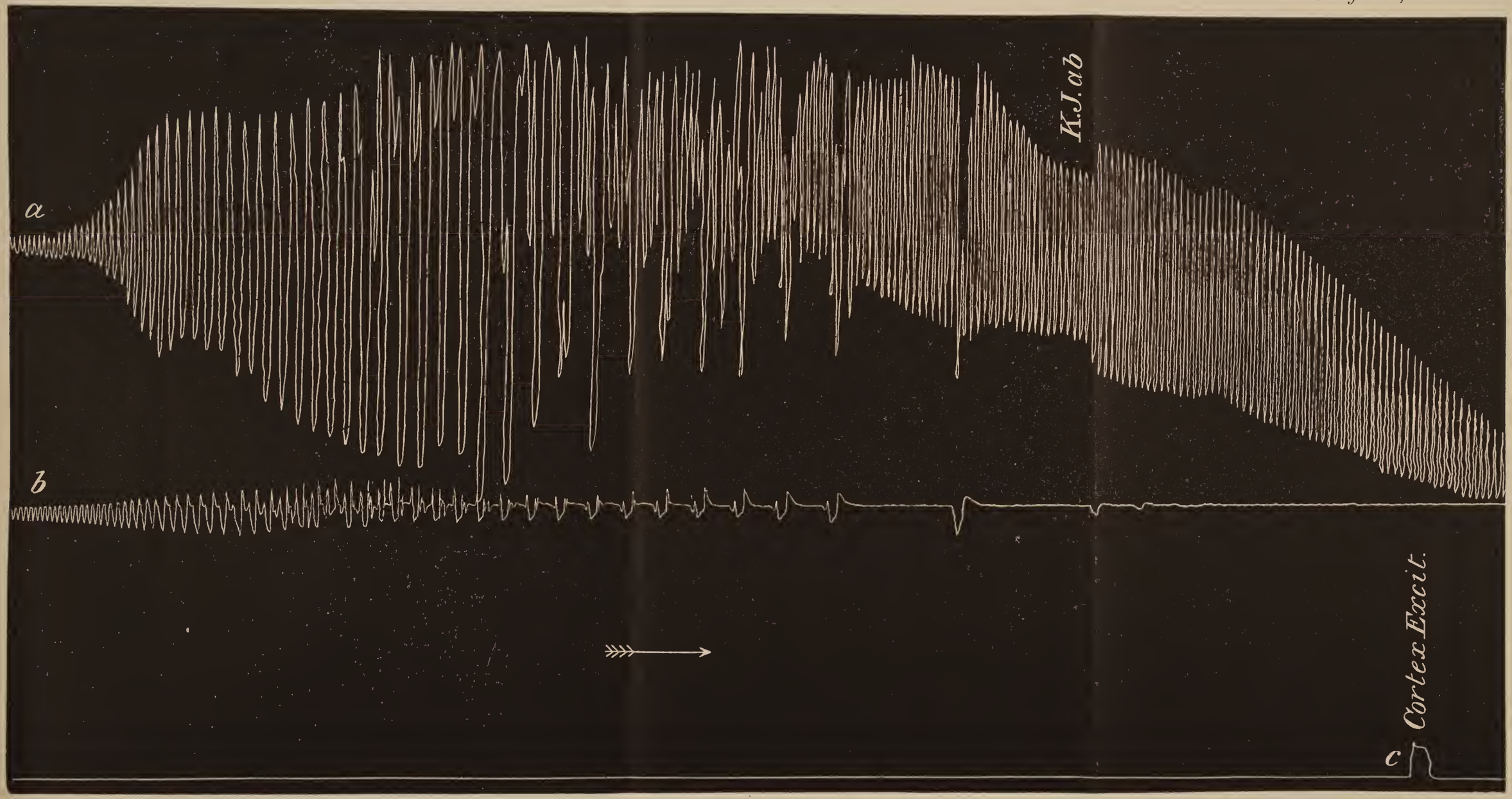
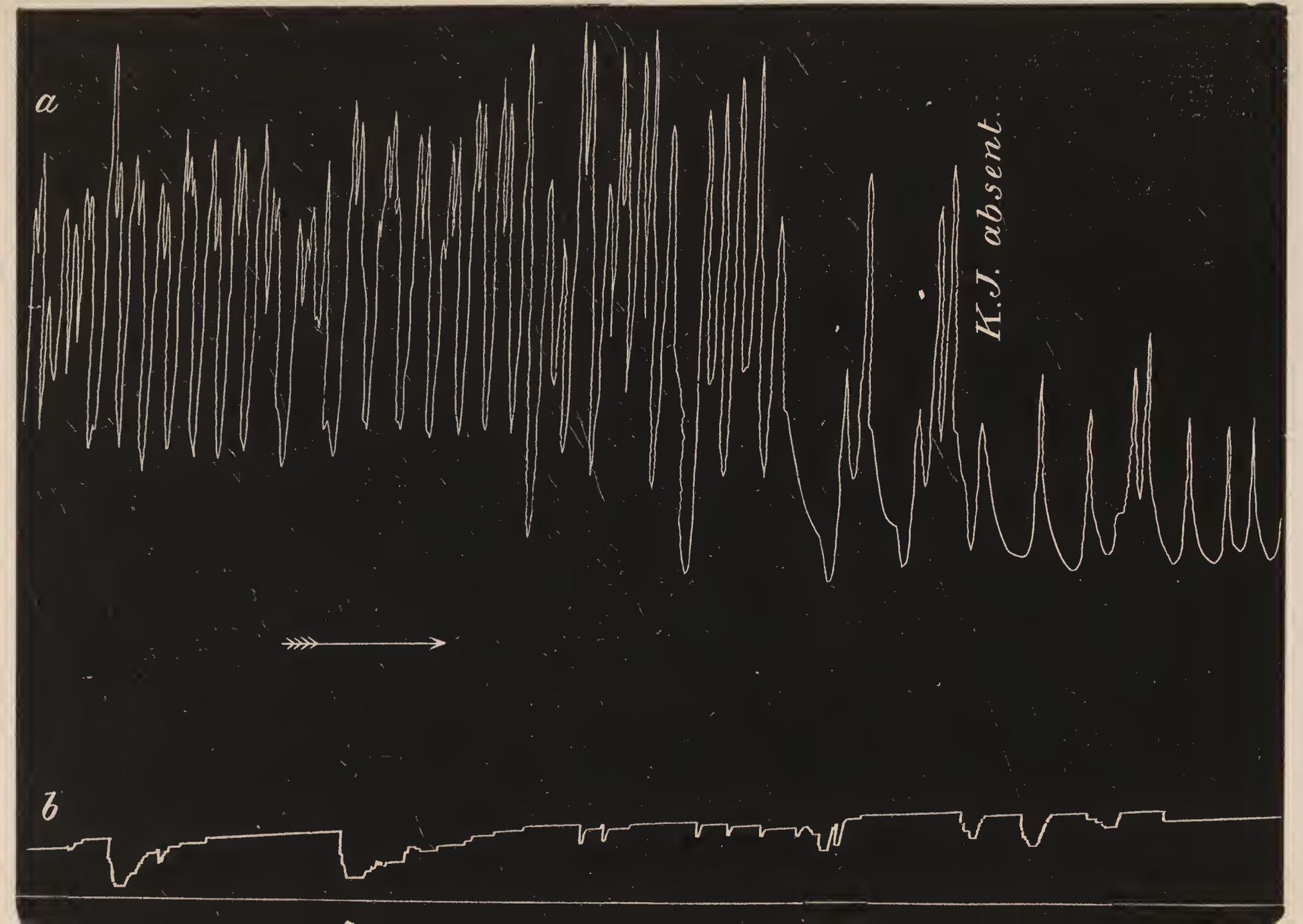


FIG. 5.




a
K.J. absent.
b

DESCRIPTION OF FIGURES.

FIG. 1 is intended to show the stages in the asphyxial state at which the knee jerks become exaggerated and are abolished.

a = Curve from carotid artery.
b = Respiratory curve.
c = Time curve.

FIG. 2 shows the stage when the knee jerk returns, after it has been abolished, and that it becomes exaggerated before returning to its normal condition.

a = Curve from carotid artery.
b = Respiratory curve.
c = Time curve.

FIG. 3 indicates the stages in the asphyxial state at which the alterations in the condition of the knee jerk occur in the rabbit.

a = Curve from carotid artery.
b = Respiratory curve.

FIG. 4 shows the stages in the asphyxial state at which the knee jerk becomes exaggerated and is abolished, and how these phenomena are related, in point of time, to the asphyxial convulsions.

a = Curve from carotid artery.
b = Respiratory curve.
c = Time curve.
d = Curve obtained from the extensor muscles of the wrist during the asphyxial convulsions.

FIG. 5 shows that a response can be obtained on excitation of the motor cortex after the knee jerk has been abolished.

a = Curve obtained from carotid artery.
b = Respiratory curve.
c = Curve obtained from extensor muscles of the wrist on a single excitation of the cortex cerebri.

FIG. 6 shows that the motor cortex remains excitable after the stage at which the knee jerk is abolished.

a = Curve from carotid artery.
b = Curve obtained from the extensor muscles of the wrist on repeated excitations of the cortex cerebri.

HARRISON AND SONS, PRINTERS IN ORDINARY TO HER MAJESTY, ST. MARTIN'S LANE.

Reprinted for the Author from the British Medical Journal,
September 23rd, 1893.

DIABETIC COMA: ITS ETIOLOGY AND SUGGESTIONS AS TO TREATMENT.

By Vaughan Harley, M.D., M.R.C.P.,
Teacher of Chemical Pathology, University College, London; and Grocer Research Scholar.

The nature of the fatal coma[1] which so frequently terminates the career of diabetic cases has failed up to the present time to receive a satisfactory explanation. As a natural consequence, the methods of treatment are entirely empirical and for the most part unsuccessful. At present I intend merely to describe a condition of coma exactly resembling the diabetic coma of man, induced by the introduction of grape sugar into the circulation of dogs, and endeavour to explain its cause.

This artificial form of coma may, I think, be considered as a truthful representative of an uncomplicated diabetic coma, seeing that it is produced by an excess of sugar alone.

I found, while working on the destruction of grape sugar in the animal body at Leipzig with Professor C. Ludwig, that if the ureters were ligatured so as to prevent any of the sugar or its products being eliminated by the kidneys, certain nervous phenomena were produced, when 8 to 12 grammes of sugar per kilo weight of dog were injected into the jugular vein in the space of about one hour. For the first ten or twelve minutes after the injection the dogs appeared perfectly well, though most of them attempted to vomit within that time; but their stomachs being empty from not having received any food during the previous twenty-four hours, they only brought up a little frothy mucus. After the lapse of these ten or twelve minutes a trembling of the skin was noticed, which, though it passed off on the animals lying down was immediately renewed in an increased form on their again standing up. This trembling of the skin was due to rapid contractions of the skin muscles. In milder cases the tremulous movement of the skin was followed by a mental drowsiness; during this condition the dog would remain in the same position for hours, though it could be roused by loud calling or shaking. After five or six hours these symptoms usually entirely passed off. In most cases the muscular movements were not limited to the skin, but passed on to the joint muscles, and gave rise to spasmodic contractions of the limbs, so that the dog was no longer able to stand.

[1] The coma arising in diabetes from complications, such as cerebral hæmorrhage, etc., will not be discussed in this paper.

The respirations were always noticed to be increased in frequency. During this nerve irritation stage, so long as the dog was conscious he would turn his head in the direction of one calling to him. Each spasm seizure usually lasted for some five minutes or so, and was followed by a longer or shorter period of repose.

In the cases in which the dogs were still more affected the muscular movements amounted to actual epileptiform convulsions, which in like manner alternated with periods of repose. During the convulsive seizures there were observed not only clonic followed by tonic spasms but likewise well marked opisthotonos. Frothy mucus would collect at the mouth. The eyelids at first opened and closed rapidly, then would become fixed, with the eyes staring wide open. The pupils became contracted, but still reacted to light. The respirations increased to 50 or 80 per minute, the pulse was unable to be counted. The animals appeared to be perfectly unconscious. This convulsive stage, which after having lasted from eight to ten minutes, was followed by a period of rest, which was again followed in from five to twenty minutes by a fresh fit. If the convulsions were very severe, which was especially the case in small and nervous dogs, the respirations would sometimes suddenly stop and the animal die. It was found that the heart continued to beat for some minutes after the respiratory movement had ceased. As a general rule the alternating convulsive and repose stage lasted from one to three hours, gradually diminishing in severity, each interval being longer, and finally the animal slowly passing into a comatose state. The comatose state, which may arise without any previous convulsive stage, begins as a rule some three or four hours after the sugar is injected, and lasts from two to six hours. When the ureters were let free during the comatose stage, in all but one case it passed off in the course of a few hours. If the ureters were not loosed, the animals as a rule died in the coma. Some few cases, however, recovered after marked coma had shown itself, even when the ureters had not been previously loosed. As it might be thought the nerve symptoms had something to do with the ligature of the ureters, it is well for me to state that from frequent experiments I found that their being ligatured caused no appreciable symptoms for at least fifteen hours. Moreover, that the nerve disturbances are not due to the presence of the sugar in an increased quantity in the blood, while in the form of sugar, is shown by the following table, which gives the quantity of sugar in the blood at various times after its injection.

The Quantity of Sugar present in the Blood at Various Time after the Injection of 10 grammes per kilo. Body Weight os Sugar, its Elimination by the Kidneys being Prevented.

Number of Experiment.	Time after Completion of Sugar Injection.	Sugar in 100 parts of Blood.
XI	Immediately	0.676
X	1 hour	0.438
V	1 hour 45 minutes	0.290
X	3 hours	0.126
XV	4 ,,	0.072
XVI	5 ,,	0.073

It is seen that immediately after the injection of the sugar while the quantity in the blood is the highest, no nerve symptoms show themselves (for at least ten minutes); they then go on increasing in severity while the sugar in the blood is decreasing for the first two to three hours, while during the fourth and fifth hour, when the quantity of sugar in the blood has fallen to normal, the coma sets in. One is, therefore, forced to conclude that the nervous disturbances are due to some substance or substances formed from the sugar after its injection. The following are the results in brief of a series of experiments made with the view of determining what these substances were :—

By quantitative analysis of the lactic acid in the blood I found (1) that its quantity was increased by the injection of sugar, and (2) that it did not tend to fall to the normal quantity as soon as the sugar did. I will give only one case as a specimen for the sake of shortening the paper.

The Quantity of Lactic Acid in the Blood after the Injection of 10 grammes per kilo. Body Weight of Sugar, its Elimination by the Kidneys being Prevented.

Number of Experiment.	Time after Completion of Sugar Injection.	Lactic Acid in 100 parts of Blood.
XI	Before injection	0.097
	Immediately after	0.134
	4 hours after	0.116
	6 ,, ,,	0.110

We here see the lactic acid is greatly increased by the sugar injection, and that it is still markedly increased even so late as the sixth hour, while I found that the sugar by the fourth hour had, as a rule, reached the normal amount. The importance of this in explaining the nervous symptoms I will consider after giving the results of some other experiments. Further, having found both aceton and aceto-acetic acid in the urine, collected after the ureters had been loosed, from five to six hours after the sugar injection, it was decided to examine the blood for these substances. From the normal blood of the dogs before the injection of the sugar no aceton, aceto-acetic acid, nor alcohol could be obtained, while from the blood of the same animals after its injection these three substances were always found.

In a series of experiments which I carried out in Turin on the respiratory gaseous changes produced by the intravenous injection of sugar,[2] I found that sugar caused an increase in the respiratory quotient of dogs during the first to fifth hour, and that after this the respiratory quotient returned to the normal about the seventh hour. The quantity of carbonic acid eliminated per minute was increased during the first hour, after which it remained about normal; the oxygen absorbed was at the same time slightly decreased.

There having been produced no nervous phenomena in the above case, it may be taken as a representation of the respiratory changes produced by an increase of sugar in the blood. On the other hand, in cases when the dogs had coma, the gaseous changes were markedly modified.

[2] On Gaseous and Temperature Changes are given in full in the *Journal of Physiology*, 1893.

Sugar Injected; its Elimination by the Kidneys being Interrupted. No Nerve Derangements.

Weight in Kilos.	Respiration Period.	Condition of Animal.	Quantity Injected.			Duration of Respiration Period in Minutes.	Total Quantity of		Amount per Minute.		$\frac{CO_2}{O_2}$
			Gms. of Sugar.		NaCl Solution.		CO_2 Eliminated.	O_2 Absorbed.	CO_2 Eliminated.	O_2 Absorbed.	Resp. Quotient
			Total.	Per Kilo.	c.c.						
5.520	a	Before sugar injection	40	7.25	80	30.0	1717.05	2588.87	57.235	86.296	0.66
	b	During first hour after				33.0	2050.64	2762.96	62.141	83.726	0.74
	c	During third hour after				40.5	2127.00	2781.38	52.519	68.675	0.77
	d	During fifth hour after				45.0	2116.20	2724.64	46.928	60.547	0.78
	e	During 7th hour after				36.5	1859.50	2681.41	50.945	73.463	0.69

Sugar Injected; its Elimination by the Kidneys being Interrupted, Profound Coma Superveniug.

Weight in Kilos.	Respiration Period.	Condition of Animal.	Quantity Injected.			Duration of Respiration Period in Minutes.	Total Quantity of		Amount per Minute.		$\frac{CO_2}{O_2}$
			Gms. of Sugar.		NaCl Solution.		CO_2 Eliminated.	O_2 Absorbed.	CO_2 Eliminated.	O_2 Absorbed.	Resp. Quotient
			Total.	Per Kilo.	c.c.						
12.500	a	Before sugar injection	122	10.0	200	23.5	1535.0	2364.52	65.319	100.53	0.65
	b	During first hour after				24.5	2095.9	2590.65	85.549	105.74	0.81
	c	During third hour after				25.0	2395.3	2595.22	95.810	103.81	0.92
	d	During sixth hour after				53.5	2619.5	2652.58	49.008	49.581	0.99
	e	During tenth hour after				100.0	2905.2	2706.50	29.052	27.065	1.07

In the above table we see that during the stage of nervous irritability which occurred within the first three hours, the carbonic acid eliminated and the oxygen absorbed was increased, the respiratory quotient being raised during the first hour from the normal 0.65 to 0.81, and during the third hour to 0.92, whereas, when profound coma set in during the sixth

hour, instead of the respiratory quotient tending to fall, as it did in the cases in which there was no coma, it continued to rise still higher till it reached 0.99. At the same time, the carbonic acid eliminated per minute was decreased to 49.008 and the oxygen absorbed fallen to 49.581. During the tenth hour (the coma continuing) the carbonic acid eliminated fell to 29.052, that is to say, less than half its original, while the amount of oxygen absorbed per minute was only 27.065, that is, a little more than a quarter of its original amount, the respiratory quotient being thus increased to 1.07.

That these marked changes in the external respiration[3] point to great alterations in metabolism is further shown by the temperature changes, for when no nervous symptoms arise, the intravenous injection of sugar causes an increase in the animal heat of about 1.5° C. = 2.7° F. If coma supervenes, however, the temperature falls. In one case it was observed to fall as much as 10.4° C. = 18.7° F. in the space of twelve and a-half hours.

Now Dr. Walter found that by giving hydrochloric acid to rabbits he was able to produce certain nerve changes in many respects resembling those above described. In his rabbits he found that the carbonic acid in the blood fell to even 2.54 volumes p. c., which roughly represents the quantity that can be simply absorbed. Normally in the blood of rabbits there is as much as 25 vol. p. c. of carbonic acid; this is supposed to be combined with the sodium carbonate and bicarbonate of the blood. He thinks that the hydrochloric acid combines with the sodium salts, and thus renders them unable to act as carbonic acid carriers. Consequently the carbonic acid accumulates in the tissues and acts as a narcotic to the nervous system.

This view is further supported by the fact of his finding that the subcutaneous injection of sodium carbonate not only prevents the symptoms occurring in rabbits, but even stops them when they have set in.

In carnivora the hydrochloric acid combines with the ammonia compounds of the prior stage to the formation of urea, and is excreted with the urine. This leads to an increase in the ammonia compounds and a diminution in the urea in the urine. The hydrochloric acid does, however, cause a slight reduction in the quantity of carbonic acid in the blood, for Walter found in one case, that of a dog, only 18.04 vol., p. c.

Hallevorden, Stabelmann, and Minkowski found that in man during diabetic coma the ammonia was increased in the urine.

My experiments lend support to this acid poisoning view, for first, acids were found in the blood, and secondly, the carbonic acid eliminated was decreased. There is, however, another factor that Walter's analysis of the blood gases did not bring out, namely, that there was a diminution in the quantity of the oxygen absorbed. If, therefore, the increase in the carbonic acid in the tissues was the cause of the narcotic symptoms, the carbon must have been oxidised by the so-called reserve oxygen of the tissues.[4]

This raises the questions: Does the diminished alkalinity of the blood reduce the power of the hæmoglobin to carry

[3] The absorption of oxygen and the elimination of carbonic acid by the lungs is termed external respiration, as distinguished from internal respiration, which is applied to the consumption of oxygen and the formation of carbonic acid in the tissues.

[4] Reserve oxygen has not yet been proved to be present in the tissues.

oxygen? Or, does the presence of alcohol, aceton, etc., and diminished alkalinity, hinder the oxidation processes in the body? My experiments strongly support the latter view, while Walter's experiments also do the same. On the other hand, my experiments give neither position nor negative support to the former view, while Walter's seem to contradict it. Another view as to the cause of diabetic coma—that the ammonia was increased in the blood—was advanced because it was found that the urine of the patients contained an excess of ammonia,

In a series of experiments I performed in Leipzig I was unable to find any increase in the quantity of the ammonia present in the blood after the intravenous injection of sugar.

Blood Distilled at 102° C. after the Addition of Magnesia, Ureters having been Ligatured.

Weight of Dog.	Ammonia obtained from 100 Parts of Blood	
	Immediately after Ureters Ligatured.	Five Hours Later.
42 kilos	0.025	0.024
Sugar Intravenously Injected after Ureters Ligatured.		
29.5 kilos	0.025	0.034
27.5 kilos	0.018	0.017

This view, therefore, can be left out of the question, as it seems to me to be without any experimental support. The experimental coma produced in dogs by the artificial introduction of sugar into the circulation may be summed up as being: 1. A stage of nervous irritation, which may be so severe as to assume the form of an epileptic convulsion, or so mild as to appear in the form of mere trembling of the skin. 2. A comatose stage which may merely amount to a few hours' drowsiness or extend to a deep coma from which the animal cannot be roused, and ending in death.

The cause of the preliminary nerve irritability stage is probably due to the formation of some as yet undetermined substance or substances acting as an irritant to the nerve centres, the comatose stage being in its turn due to the effects of various toxic substances combining to produce it. The alcohol and the aceton derived from the splitting up of the sugar molecule may be partly the cause of the diminished oxidation. The coma seems, however, to be principally due to a diminution in the alkalinity of the blood produced by the acid products derived from the breaking up of the sugar molecule, the acids combining with the sodium carbonate and bicarbonate as well as with the ammonia in the blood, and thus hindering the blood carrying the carbonic acid to the lungs for elimination; while there is at the same time a diminution in the oxygen absorbed, and thus the oxidation in the organism is hindered from being properly carried on by a process of tissue asphyxia.

The artificial coma produced in the foregoing experiments, while it is seen to be exactly analogous to that occurring in diabetic patients, does not appear to depend upon an increase in the quantity of the sugar in the organism, but upon the increase that has taken place in its derivatives. In all

probability the same products are being continually formed in the healthy body, but only in such small quantities and so gradually that they are either sufficiently rapidly eliminated or there is sufficient time for them to be further transformed, in the process of metabolism, into harmless substances, and consequently are never present in the blood in an amount capable of producing coma.

In the cases of diabetes due to diminished assimilation of the sugar in the organism, such as pancreatic diabetes, coma occurs when the sugar has disappeared from the urine. The presence of the sugar in the urine arose from the organism being unable to assimilate all the sugar normally formed, the disappearance of the sugar from the urine being either due to its being no longer formed in normal quantity or to the organism having recovered the power of breaking its molecule down. From some cause as yet undiscovered the normal power of breaking down the sugar molecule in the ordinary processes of metabolism has been regained, and since the quantity of sugar present both in the tissues and blood had been previously increased, an excess of its products is produced, and hence the coma. This point is of great importance in practice, as it indicates that one ought always to be on the outlook for coma whenever a diabetic patient's urine ceases to contain sugar, if its disappearance cannot be accounted for either by dietetic or other treatment. By analysing the urine and finding aceton, or aceto-acetic acid, as well as making quantitative estimation of the ammonia and lactic acid present in it, one may be able not only to predict the onset of coma, but prevent it. The urine should be further examined for β-oxybutyric acid, for although in my experimental coma I never found it either in the urine or the blood, it has been so frequently found present in patients' urine that its presence is of significance and ought to be looked for.

The preliminary stage of nerve irritation is frequently manifested as a premonitory sign in man, by well-marked delirium, vomiting, or twitchings of the hands; in some cases even convulsions have been referred to.

As regards the treatment of diabetic coma, no remedy having been as yet discovered for the terminal comatose stage of diabetes—though there have been no lack of proposals—I need not take up time by reviewing them, except to say that the most praised have been the citrated alkalies given in drachm doses.

Conclusions as to Treatment.

The rational treatment founded on the results obtained from the above-mentioned experiments is to administer alkalies. If the symptoms are urgent and time is of moment, sodium carbonate might be administered subcutaneously or intravenously, as recommended by Stabelmann, the pulse being carefully watched in case of heart failure. At the same time, since my experiments have shown so great a diminution in the oxygen absorbed, it is advisable to encourage oxidation. The inhalation of pure oxygen may help, as well as trying to improve oxidation by massage. Diuretics, together with large quantities of fluids, will be of value in increasing the rapidity of the elimination of the toxic products derived from the sugar. These are the means I venture to suggest to ward off attacks of diabetic coma, or even to diminish the severity of a coma already set in.

[*From the Journal of Physiology. Vol. XV. No.* 3, 1893.]

INFLUENCE OF SUGAR IN THE CIRCULATION ON THE RESPIRATORY GASES AND ANIMAL HEAT.

By VAUGHAN HARLEY, M.D., M.R.C.P., *Grocer Research-Scholar. Teacher of Chemical Pathology, University College, London.* (Plates III., IV., V.)

(*From the Physiological Institute, Turin.*)

Having in previous papers[1] shown that when grape-sugar is brought into contact either with defibrinated or non-defibrinated blood freshly withdrawn from healthy animals, such as the calf, rabbit, dog etc., it gradually disappears. And that this disappearance of sugar from blood though partly owing to some of it becoming entangled with the albumens during their coagulation (mechanical retention) is mainly due to its being transformed into some other product or products. Also that the amount of sugar that disappears is proportional to the time it is in contact with the blood. And from finding that this still occurs in the absence of bacteria, it seemed to me probable that the disappearance of the sugar is due to its being split up and transformed into some other materials through the influence of an enzyme.

On further extending the observations (in the Physiological Institutes of Christiania and Leipzig,) to the part played by grape-sugar artificially introduced into the living circulation, I found, in accordance with the results of Limpert and Falck[2], as well as those of Brasol[3], that the greater part of the sugar injected into the veins of a living animal is not excreted by the kidneys; but remains behind in the organism.

I likewise observed that when 5 or 6 grams of grape-sugar per kilo of animal weight, are introduced into the jugular veins of dogs or

[1] Vaughan Harley. "The behaviour of saccharine matter in the Blood." This *Journal*, Vol. XII. p. 391, 1891. Also "Pathogenesis of Pancreatic diabetes." *Brit. Med. Journal*, Aug. 27, 1892.

[2] Limpert u. Falck. *Virchow's Archiv*, Vol. IX. p. 56, 1856.

[3] Brasol. "Wie entleidigt sich das Blut" etc. *Archiv f. Physiol.* p. 211, 1884.

rabbits, it diminishes so rapidly that in from 1 to 2 hours the quantity of the sugar in the blood is restored to its normal amount.

The diminution of the sugar under these circumstances was shown by Weyert[1] not to be due to renal elimination; for when the ureters are ligatured previous to the injection, the quantity of sugar in the blood is still greatly reduced in the short space of three hours.

This disappearance of the sugar cannot be accounted for on the supposition of its having been either deposited, as such, in the tissues or of its having been transformed (as stated by other observers) into glycogen. For in no case whatever did I find a sufficient increase either in the quantity of sugar or glycogen in the liver or muscles to account for the loss of the sugar.

In a later series of experiments performed in the laboratory of Prof. C. Ludwig (where Brasol and Weyert carried out theirs) I found, that as much as 10 grams of grape-sugar per kilo weight of dog, could be injected into the circulation after ligaturing the ureters and yet the quantity present in the blood fall to the normal, and in most cases even to less than the normal standard within from 5 to 6 hours after the injection had been made.

It may be remarked that the ligature of the ureters seems to cause an almost instantaneous stoppage of the urinary excretion. For on killing dogs within an hour after the operation, the kidneys and their surroundings are found to be œdematous, and though the ureters above the seat of ligature are filled with liquid, since the liquid contains no urea it ought to be regarded rather as lymph than urine. The œdematous condition of the parts subside in from 2 to 4 hours, and within 5 hours after the ligatures have been applied, there is not only no longer any œdema to be found in the kidneys or their surroundings, but their tissues all appear to be normal when carefully examined both macro- and micro-scopically.

The effects of injection of grape-sugar into the jugular vein of dogs, are the following:—

Increased frequency of respiration. (Amounting even in some cases to actual panting.) The blood is more watery (as is shown by estimating the percentage of hæmoglobin before and after the injection). And from the amount of liquid injected being in no case alone sufficient to account for this dilution one is led to suppose that a withdrawal of liquid from the tissues into the blood vessels has been produced by the

[1] Weyert. "Der Übergang des Blutzuckers in verschiedene Korkersalze." *Ibid.* p. 187, 1891.

increase in the specific gravity of the blood owing to the introduction of the sugar.

The blood pressure (as estimated by Ludwig's kymograph,) rises pari passu with the introduction of the sugar solution: and continues after its injection has ceased. This is owing, I think, to the above alluded to absorption of liquid from the tissues taking place.

Both the blood pressure and the fluidity of the blood gradually return to their normal conditions as the excess of sugar disappears from the circulation.

The urine, which is greatly increased in quantity, at first contains much sugar. The amount not only varying with the quantity of sugar injected but likewise according to the idiosyncrasy of the animal.

Sugar continues to be excreted, though only in small quantities, by the kidneys long after the amount circulating in the blood has fallen to within the normal standard (0·05 to 0·15 p.c.). In some cases sugar may be detected in the urine for 24 hours after its injection.

In no case do the animals appear greatly inconvenienced by the injection of even as much as 10 grams of grape-sugar per kilo of bodily weight so long as the urinary excretion is not interfered with.

When on the other hand the ureters are ligatured previous to the injection of the sugar, and its elimination by the kidneys thus interrupted, the animals suffer more or less from nerve symptoms. These vary not only according to the amount of sugar injected but apparently also according to the animals' constitutional susceptibility.

When after ligaturing the ureters, from 3 to 6 grams of grape-sugar per kilo of animal weight are injected into the jugular, the same effects as regards blood pressure and fluidity of the blood are observed as those described as having occurred without the appearance of any nervous symptoms when the elimination of the sugar was not interfered with. Whereas after the injection of from 6 to 8 grams, there are often seen nerve disturbances—as indicated by muscular spasms, in some cases followed by a semi-comatose state.

When larger quantities of sugar (8 to 10 grams) are injected they always produce the spasms which in some cases assume the appearance of even typical epileptic fits; which when they are not severe enough to cause immediate death are followed by a comatose condition, often ending fatally. This comatose state resembles that of diabetic coma.

The sugar injected must have either been used up in the tissues of the animal as sugar, or have been converted into some other substance or substances not yet recognised. This is shown by the fact that if

after the ureters had been ligatured for 6 hours, the ligatures were removed, the urine then excreted contained no sugar.

The knowledge of these facts led me to endeavour to ascertain if the sugar was split up into carbonic acid in the tissues and eliminated as such by the lungs.

The following results obtained from a series of experiments conducted in the Physiological Institute of Turin with the purpose of ascertaining the effects of sugar on the respiratory gases and animal heat bear out this view.

Before proceeding further, I must acknowledge the great obligation I am under to Prof. Mosso for his kindness in not only placing his laboratory but all the necessary apparatus and materials for the enquiry at my disposal, as well as to Dr Grandis for the untiring personal assistance he gave me throughout the series of experiments.

The method of procedure which I adopted was as follows:—In order that the whole of the respired gases should pass through the respiratory apparatus employed, tracheotomy was performed, and the trachea directly connected with it.

The respiratory apparatus was made on the same principle as that invented and used by Prof. Ludwig[1], though somewhat modified by Dr Grandis in order to enable it to be used for longer periods and for larger animals. The expired air was passed into a vessel containing a solution of barium hydrate of known strength to absorb the carbonic acid, the volume of this absorbed carbonic acid being replaced by an equal volume of oxygen. Thus although the animal breathed the same nitrogen over and over again it had a continuous supply of fresh oxygen to replace the expired carbonic acid.

As the quantity of oxygen taken into the lungs is greater than the amount of carbonic acid eliminated, in all cases where the respiratory changes are calculated it being necessary to know the quantity of both, the respiratory quotient was estimated by dividing the quantity of carbonic acid eliminated by the amount of oxygen absorbed.

For the analysis of the oxygen the apparatus of Petterson and Sonden[2] was employed, the carbonic acid was calculated by titration after the method of Pettenkofer, and its volume estimated from the quantity found.

The volumes of all the gases were corrected to 0° C. and 760 mm. Hg. of barometric pressure.

[1] Sanders-Ezn. *Arbeit. d. physiol. Anst. zu Leipzig*, 1868; p. 58.
[2] Petterson and Sonden. *Zeit. für Instrumentenkunst*, p. 472, 1889.

From its being known that muscular movements[1] increase the elimination of carbonic acid, in order to reduce them to a minimum, the animal was carefully fixed with broad bandages to a cushion. The thus fixing the animals had a double advantage; for while it secured almost complete muscular rest the bandages at the same time hindered the loss of animal heat.

All the sugar used in the experiments was chemically pure grape-sugar, dissolved in normal saline (0·75 per cent. sodium chloride) solution. And a 50 per cent. solution was employed in order to avoid, as much as possible, the introduction of inconveniently large quantities of fluid into the circulation. In all cases, it was injected into a jugular vein, and as a rule at the temperature of 39° C. and at the rate of about 2 grams of sugar per minute. In order to ascertain the influence the sugar had on the bodily temperature a thermometer was kept in the animal's rectum and a reading taken every 5 minutes.

When in order to prevent any of the sugar being eliminated by the kidneys, it was necessary to ligature the ureters, it was found to be easiest done by making an incision, along the outer edge of the rectus muscle, a little above Poupart's ligament, sufficiently large to allow of the entrance of two fingers. On passing a finger along the brim of the pelvis it comes in contact with the ureter as it crosses the iliac artery on its way to reach the bladder. At this point the ureter can be readily withdrawn from the wound and ligatured. It is then replaced in the abdomen and the wound stitched up. The same mode of procedure was followed in ligaturing the ureter on the opposite side. The whole operation occupies but a few minutes and is unattended with hæmorrhage, or any disturbance to the alimentary canal.

As it was pointed out by Regnault and Reiset[2] that the respiratory quotient not only varies in different animals, but also in the same species, and even in the same animal under various circumstances; such as rest, food etc., I have in the following table noted the effects of diet on the respiratory changes in nine different dogs.

Here it is seen that dogs on the day following a carbohydrate diet have a respiratory quotient of from 0·77 to 0·78. The dogs of Regnault and Reiset on a similar diet had a somewhat higher respiratory quotient, namely from 0·91 to 0·94. And while my dogs on a meat

[1] Chaveau et Kaufmann. *Comptes Rendus*, Vol. CIII. p. 1057, 1886; and Vol. CIV. p. 1126 and 1532; 1887, and others.

[2] Regnault and Reiset. *Ann. d. Chim. et Phys.* (3), Vol. XXVI. 1849.

TABLE I.

Showing the effects of various dietetic conditions on the Respiratory quotient in Dogs.

No. of exp.	Weight in kilos	Condition as to food	Duration of respiratory periods in mins.	Total quantity of		Amount per minute		Resp. quotient $\frac{CO_2}{O_2}$
				CO_2 eliminated	O_2 absorbed	CO_2 eliminated	O_2 absorbed	
I	4·100	Carbohydrate diet previous day	46·50	1706·50	2215·70	36·70	47·65	0·77
II	5·350	Ditto	36·50	1512·80	1942·70	41·45	53·23	0·78
III	5·520	Previous day meat diet	30·0	1717·05	2588·87	57·24	86·30	0·66
IV	12·500	Ditto	23·5	1535·00	2364·52	65·32	100·53	0·65
V	3·070	Ditto	36·5	1306·60	1970·53	35·79	53·99	0·66
VII	1·850	Fasted one day	18·5	394·92	610·61	21·35	33·01	0·65
VIII	4·600	Fasted about five days	31·0	1657·5	2771·45	53·47	89·40	0·59
IX	12·500	Ditto	17·0	1488·1	2631·9	87·54	154·82	0·57
VI	15·000	Fasted more than seven days	15·0	1056·0	2272·71	70·40	151·51	0·48

diet gave a respiratory quotient of from 0·65 to 0·66; they have estimated theirs at from 0·74 to 0·75.

It is shown in the last four cases in the above table the fasting periods exert a great influence on the respiratory quotient. For while the dog that fasted only one day had a respiratory quotient of 0·65, the one that fasted seven days had a quotient of 0·48 and the two others after five days' fasting intermediate respiratory quotients of 0·57, and 0·59 respectively.

Seeing that the respiratory quotient differed so widely in different cases it was thought necessary, before the effects of sugar in any given case were considered, to perform a preliminary test experiment in order to find what the actual normal quotient of the dog under examination was, so that it might be used as a standard of comparison in calculating the results obtained from the sugar experiment.

Sugar injected into the circulation while its elimination by the kidneys was interrupted—

After the ureters had been ligatured and tracheotomy performed the animal was allowed 20 minutes' repose, in order to allow the immediate effects of the operation to pass off.

Then the trachea was connected with the respiratory apparatus and

the 'normal standard' of respiration ascertained. The sugar solution was now injected, in the manner above described, and the standard thus found compared with the normal one.

TABLE II. Experiment 1.

Weight in kilos	Respiration period	Condition of animal	Quantities injected			Duration of resp. period in mins.	Total quantities of		Amount per minute		Resp. quotient $\frac{CO_2}{O_2}$
			grams of sugar		NaCl solution		CO_2 eliminated	O_2 absorbed	CO_2 eliminated	O_2 absorbed	
			total	per kilo							
4·100	a	Before injection of sugar	41·0	10·0	80 c.c.	46·5	1706·5	2215·7	36·701	47·649	0·77
	b	During 1st hour after sugar injection				45·0	2126·2	2330·4	47·251	51·786	0·91

In the above table it is seen that during the first hour after injection of 10 grams of grape-sugar per kilo of dog into the jugular vein the respiratory quotient had risen from 0·77 to 0·91, and that the increase of the respiratory quotient occurred in spite of the oxygen absorbed being increased during the first hour after the sugar injection. For while this dog normally used up 47·649 c.c. of oxygen to form 36·701 c.c. of carbonic acid per minute, the sugar caused it to absorb 51·786 c.c. of oxygen in forming 47·251 c.c. of carbonic acid per minute. From this it seems as if some of the sugar was almost immediately transformed in the organism into carbonic acid.

This result led to the consideration of the question of how long the increase in the elimination of carbonic acid would last. With the object of ascertaining this point in the next experiment the respiration was taken a third time, during the third hour after the injection of the sugar.

In Table III., as in Table II. it is seen that the quantities of oxygen absorbed and of carbonic acid eliminated were increased during the first hour following upon the intravenous injection of 10 grams of grape-sugar per kilo.

In this case during the normal respiration of the dog 53·225 c.c. oxygen went to form 41·446 c.c. carbonic acid, while after the injection of sugar into his blood 50·380 c.c. of oxygen formed 45·970 c.c. carbonic acid gas. The respiratory quotient was therefore increased from 0·78 to 0·91 in the first hour. During the third hour however the oxygen absorbed fell to 40·797 c.c., notwithstanding that the carbonic acid

TABLE III. Experiment 2.

Sugar injected. Its elimination by the kidneys being interrupted. Some slight nerve derangements, but no coma.

Weight in kilos	Respiration period	Condition of animal	Quantity injected: grams of sugar total	Quantity injected: grams of sugar per kilo	Quantity injected: NaCl solution	Duration of resp. period in mins.	Total quantity of: CO_2 eliminated	Total quantity of: O_2 absorbed	Amount per minute: CO_2 eliminated	Amount per minute: O_2 absorbed	Resp. quotient $\frac{CO_2}{O_2}$
5·350	a	Before sugar injection	53·5	10·0	106·5 c.c.	36·5	1512·8	1942·7	41·446	53·225	0·78
	b	During first hour after				29·0	1333·3	1461·1	45·970	50·380	0·91
	c	During third hour after				29·0	1239·9	1183·1	42·755	40·797	1·05

eliminated still remained above the normal standard: being 42·755 c.c. This gave the yet higher respiratory quotient of 1·048. It consequently appears that more carbonic acid is given off in the third hour than during the first after the injection of sugar.

In order therefore to discover at what time the greatest elimination of carbonic acid takes place, as well as to judge if, as I found the sugar did in the blood, it returned to the normal standard after the sixth hour, I decided to prolong the experiments.

TABLE IV. Experiment 3.

Sugar injected. Its elimination by the kidneys being interrupted. No nerve derangements.

Weight in kilos	Respiratory period	Condition of animal	Quantity injected: grams of sugar total	Quantity injected: grams of sugar per kilo	Quantity injected: NaCl solution	Duration of resp. period in mins.	Total quantity of: CO_2 eliminated	Total quantity of: O_2 absorbed	Amount per minute: CO_2 eliminated	Amount per minute: O_2 absorbed	Resp. quotient $\frac{CO_2}{O_2}$
5·520	a	Before sugar injection	40	7·25	80 c.c.	30·0	1717·05	2588·87	57·235	86·296	0·66
	b	During first hour after				33·0	2050·64	2762·96	62·141	83·726	0·74
	c	During third hour after				40·5	2127·00	2781·38	52·519	68·675	0·77
	d	During fifth hour after				45·0	2116·20	2724·64	46·928	60·547	0·78
	e	During 7th hour after				36·5	1859·50	2681·41	50·945	73·463	0·69

We have here (Table IV.) the carbonic acid increased, as in the former cases; although in order to avoid muscular spasms or a comatose state supervening, which might complicate the results, only 7·25 grams of grape-sugar per kilo were injected.

It is seen that before the injection of the sugar 86·296 c.c. of oxygen formed 57·235 c.c. of carbonic acid, giving a quotient of 0·66, while the first hour following the injection less oxygen was absorbed: as 83·726 c.c. of oxygen formed 62·141 c.c. carbonic acid, thus giving the higher quotient of 0·74. During the third hour again, as in Table III., not only was less carbonic acid eliminated than during the first hour; but also less than during the normal respiratory standard. However from the oxygen absorbed being at the same time more markedly decreased the respiratory quotient had risen to 0·77. During the fifth hour the carbonic acid eliminated decreased to 46·928 c.c., and the oxygen absorbed fell to 60·547 c.c., thereby giving the still higher quotient of 0·78. This result may have however been partly due to an accident, as the dog's breathing stopped towards the end of the respiratory period. This arrest of the breathing was found to be due to asphyxia produced by the barium solution having become saturated with carbonic acid. Be that as it may, during the seventh hour the quantity of oxygen absorbed to form 50·945 c.c. carbonic acid had risen to 73·463, thus giving the smaller respiratory quotient of 0·69; a near approach to the normal standard found in this dog before the injection of the sugar.

In the following two cases the dogs suffered from coma as a consequence of the sugar injection.

TABLE V. EXPERIMENT 9.

Sugar injected. Its elimination by the kidneys being interrupted; followed by a comatose condition.

Weight in kilos	Respiration period	Condition of animal	Quantity injected grams of sugar total	per kilo	NaCl solution	Duration of resp. period in mins.	Total quantity of CO_2 eliminated	O_2 absorbed	Amount per minute CO_2 eliminated	O_2 absorbed	Resp. quotient $\frac{CO_2}{O_2}$
12·500	a	Before sugar injection	100·0	8·0	200 c.c.	17·0	1488·1	2631·9	87·537	154·82	0·57
	b	During 1st hour after				24·5	1799·4	2501·7	73·448	102·11	0·72
	c	During 3rd hour after				35·0	1918·5	2651·6	54·815	75·760	0·72
	d	During 7th hour after				71·0	1726·2	2498·2	24·313	35·186	0·69

This dog (Table V.), which had been fasting some days, had a normal respiratory quotient of 0·57. After the sugar injection instead of 154·82 c.c. oxygen forming 87·537 c.c. carbonic acid, 102·11 c.c. of oxygen formed 73·448 c.c. carbonic acid, thus raising the quotient to 0·72. The case is somewhat exceptional; for although only 8 grams of grape-sugar per kilo of body weight were injected the animal became comatose.

The oxygen absorbed, as will be noticed, steadily decreased in each successive respiratory period (*b*, *c*, *d*,) while the carbonic acid eliminated also decreased, though not in so marked a ratio. The respiratory quotient which in the third had remained as during the first hour at 0·72, during the seventh had fallen to 0·69. Thus shewing a tendency to return to the normal.

In the next case in which 10 grams of sugar per kilo were injected after ligaturing the ureters, there was profound coma, and it was the only one met with in which the respiratory quotient showed no tendency to return to the normal after the sixth hour.

TABLE VI. Experiment 4.

Sugar injected. Its elimination by the kidneys being interrupted; profound coma supervening.

Weight in kilos	Respiration period	Condition of animal	Quantity injected			Duration of resp. period in mins.	Total quantity of		Amount per minute		Resp. quotient $\frac{CO_2}{O_2}$
			grams of sugar		NaCl solution		CO_2 eliminated	O_2 absorbed	CO_2 eliminated	O_2 absorbed	
			total	per kilo							
12·500	a	Before sugar injection	122	10·0	200 c.c	23·5	1535·0	2364·52	65·319	100·53	0·65
	b	During 1st hour after				24·5	2095·9	2590·65	85·549	105·74	0·81
	c	During 3rd hour after				25·0	2395·3	2595·22	95·810	103·81	0·92
	d	During 6th hour after				53·5	2619·5	2652·58	49·008	49·581	0·99
	e	During 10th hour after				100·0	2905·2	2706·5	29·052	27·065	1·07

In the normal respiration it is seen (Table VI.) in this case that 100·53 c.c. oxygen formed 65·319 c.c. of carbonic acid thereby giving a quotient of 0·65. Whereas on 10 grams of sugar per kilo being injected it took during the first hour only 105·74 c.c. of oxygen to form 85·549 c.c. of carbonic acid. The quotient yielded being 0·81. During the third hour, 103·81 c.c. of oxygen formed 95·810 c.c. of carbonic acid,

thereby increasing the respiratory quotient to 0·92. Coma then set in, and the temperature steadily fell. And in 11 hours after the sugar was injected it had fallen from 37·04° to 28·62° C.; that is to say 8·42° C.

In the respiratory period (*d*), six hours after the injection of the sugar, only 49·581 c.c. of oxygen were absorbed per minute, yielding 49·008 c.c. of carbonic acid, thus giving the high quotient 0·99. While during the 10th hour only 27·065 c.c. of oxygen were absorbed, yielding 29·052 c.c. of carbonic acid, thereby raising the respiratory quotient to the still higher figure of 1·07.

Being anxious to exclude as far as possible every avoidable source of error in estimating the influence sugar has on the respiratory gases and animal heat, with the view of ascertaining how much of the effects observed was due to the mere injection of the saline solution, and operative procedure, independent of the sugar introduced into the circulation, the following experiment was made.

TABLE VII. Experiment 6.

Ureters ligatured. Normal saline solution was only injected. Neither spasms nor coma supervened.

Weight in kilos	Resp. period	Condition of animal	Quantity of NaCl solution injected	Duration of resp. period in mins.	Total quantity of		Amount per minute		Resp. quotient $\frac{CO_2}{O_2}$
					CO_2 eliminated	O_2 absorbed	CO_2 eliminated	O_2 absorbed	
15·000	a	Before saline injection	300 c.c.	15·0	1056·0	2272·71	70·401	151·51	0·48
	b	During 1st hour after	i.e. 20 c.c. per kilo	17·0	1442·3	2247·23	84·843	132·19	0·64
	c	During 3rd hour after		16·0	1243·7	2150·24	77·911	134·39	0·58
	d	During 7th hour after		18·5	1035·4	2245·34	55·966	121·37	0·47
	e	During 12th hour after		17·0	952·96	2050·85	56·057	120·65	0·47

In the above Table VII. it is seen that the mere injection of what is called a physiological normal saline solution causes of itself increased tissue changes. This is shown by there being an increase of the carbonic acid eliminated, even without the oxygen absorbed being increased. For while during the normal test experiment 151·51 c.c. of oxygen caused the elimination of 70·401 c.c. of carbonic acid, during the first hour after the saline injection 132·19 c.c. of oxygen produced 84·843 c.c. of carbonic acid. The respiratory quotient 0·48 being thereby increased to 0·64. During the third hour again 134·39 c.c. of

oxygen yielded 77·911 c.c. of carbonic acid giving the smaller respiratory quotient 0·58. And during the seventh hour 121·37 c.c. of oxygen caused the elimination of 55·966 c.c. of carbonic acid giving a still smaller respiratory quotient of 0·47. And again during the 12th hour 120·65 c.c. of oxygen formed 56·057 c.c. of carbonic acid with the quotient 0·47. That is to say the quotient was during the seventh and the twelfth hour after the same as it had been before the saline injection. It is further seen that the oxygen absorbed steadily fell during each successive respiratory period, and that at the same time, except during the periods *b* and *c*, the carbonic acid eliminated likewise fell below what was found in the normal standard.

One must therefore admit that saline solution itself causes an increased elimination of carbonic acid. But instead of its doing so during many hours as in the case of the sugar, it begins to fall before the third hour, the very time when the effects of the sugar injection on the respiratory quotient are most marked. Further, after the immediate effect of the saline solution has passed off, the respiratory quotient returns to the normal standard; at which it remains for at least 12 hours.

One must from this conclude that although the mere injection of saline solution along with the sugar may account for some of the increase of the respiratory quotient during the first hour, it does not do so for the increase during the subsequent hours.

The ligaturing of the ureters for more than 13 hours appears to have no influence whatever on the respiratory quotient. For as it is seen in Table VII. instead of being most marked when they have been longest ligatured, we find that at the eighth and thirteenth hour (*d* and *c*) after the ureters have been ligatured the quotient is at its normal.

Thus we see that when sugar is injected after the ureters have been ligatured so as to prevent any of it escaping from the blood by means of the kidneys, there is an increase in the amount of carbonic acid eliminated by the lungs. This increased elimination begins in the first hour after the injection of the sugar and steadily increases up to the fifth hour, when it gradually begins to return to the normal; which it reaches about the seventh hour as seen in Table IV. The only exception to this gradual return of the respiratory quotient to the normal standard was met with in Experiment 4 (Table VI.) where there was marked coma associated with an extreme fall in the temperature (8·42° C.), owing no doubt to a diminution in the tissue oxidation caused by the coma.

Effects of sugar injected into the circulation while its elimination by the kidneys is not interfered with.

This series of experiments was performed with the view of ascertaining what would be the effects on respiration and temperature of sugar artificially introduced into the circulation, if it were allowed to be eliminated by the kidneys along with the urine. The modes of operative procedure were in every respect identical to those adopted in the previous cases—with the single exception that the ureters were not ligatured. In all the experiments 10 grams of grape-sugar per kilo of the animal's weight were employed.

TABLE VIII. Experiment 7.

Sugar injected without its elimination by the kidneys being interfered with.

Weight in kilos	Respiratory period	Condition of animal	Quantity injected: grams of sugar total	Quantity injected: grams of sugar per kilo	Quantity injected: NaCl solution	Duration of resp. period in mins.	Total quantity of CO_2 eliminated	Total quantity of O_2 absorbed	Amount per minute CO_2 eliminated	Amount per minute O_2 absorbed	Resp. quotient $\frac{CO_2}{O_2}$
1·850	a	Before sugar injection	18·0	10·0	36 c.c.	18·5	394·92	610·61	21·35	33·01	0·65
	b	During 1st hour after				21·0	466·01	683·20	22·19	32·53	0·68
	c	During 3rd hour after				17·0	408·09	583·45	24·01	34·62	0·69
	d	During 6th hour after				18·0	439·68	575·07	24·43	31·95	0·77
	e	During 9th hour after				16·0	444·94	567·25	27·81	35·45	0·78

In the above Table VIII. it is seen that 33·01 c.c. of oxygen was sufficient to form 21·35 c.c. of carbonic acid and gave a quotient of 0·65 as the normal respiration standard, while during the first hour after the sugar injection 32·53 c.c. of oxygen formed 22·19 c.c. of carbonic acid, thus raising the quotient to 0·68. This in the third hour was still further increased; for 34·62 c.c. of oxygen then formed 24·01 c.c. of carbonic gas and gave a quotient of 0·69. During the sixth hour 31·95 c.c. of oxygen formed 24·43 c.c. of carbonic acid and gave the quotient 0·77. Instead however of falling, as it had in the previous series of experiments after the sixth hour. During the ninth hour 35·45 c.c. of oxygen yielded 27·81 c.c. of carbonic acid thereby giving the still higher quotient of 0·78.

The urine passed by this dog during the ninth hour still contained sugar; just as it had done immediately after the sugar injection.

TABLE IX. Experiment 5.

Sugar injected without its elimination by the kidneys being interrupted.

Weight in kilos	Respiratory period	Condition of animal	Quantity injected: grams of sugar total	Quantity injected: grams of sugar per kilo	Quantity injected: NaCl solution	Duration of resp. period in mins.	Total quantity of CO_2 eliminated	Total quantity of O_2 absorbed	Amount per minute CO_2 eliminated	Amount per minute O_2 absorbed	Resp. quotient $\frac{CO_2}{O_2}$
3·070	a	Before sugar injection	30·0	10·0	60 c.c.	36·5	1306·6	1970·5	35·79	53·99	0·66
	b	During 1st hour after				57·0	1687·0	2537·3	29·60	44·51	0·67
	c	During 4th hour after				50·0	2070·8	2841·3	41·42	56·83	0·73
	d	During 7th hour after				56·0	1863·5	2295·2	33·28	40·98	0·81

In Table IX., we find the same gradual rise in the respiratory quotient that occurred in the previous case. During the ninth hour the quantity of carbonic acid formed per minute is somewhat less than that during the normal respiration, but as the oxygen is also decreased the quotient has risen, instead of falling as it did in the cases where the ureters were ligatured.

TABLE X. Experiment 8.

Sugar injected without its elimination by the kidneys being interfered with.

Weight in kilos	Respiratory period	Condition of animal	Quantity injected: grams of sugar total	Quantity injected: grams of sugar per kilo	Quantity injected: NaCl solution	Duration of resp. period in mins.	Total quantity of CO_2 eliminated	Total quantity of O_2 absorbed	Amount per minute CO_2 eliminated	Amount per minute O_2 absorbed	Resp. quotient $\frac{CO_2}{O_2}$
4·600	a	Before sugar injection	46·0	10·0	92 c.c.	31	1657·5	2771·5	53·47	89·40	0·59
	b	During 1st hour after				49	1900·2	2702·9	38·78	55·16	0·70
	c	During 4th hour after				72	2120·3	2685·6	29·44	37·30	0·78

Here again in (Table X.) we have the same increase in the respiratory quotient caused by the injection of sugar as in the former two cases.

It is thus evident that when the injected sugar, is allowed to be excreted by the kidneys, the rise in the respiratory quotient during the first 3 or 4 hours is not so marked, as when it is prevented doing so. And further that instead of the quotient returning to the normal after

the sixth hour, as it did (Tables IV. and V.) when the ureters were ligatured, it (Tables VIII. and IX.) somewhat increased. In these three cases the urine continued to contain sugar up to the end of each of the experiments, and in none was there any nervous symptoms, neither muscular twitchings, convulsions, nor the slightest coma having shown itself.

Influence of grape-sugar on animal heat.

From the fact of the development of animal heat being the direct result of chemical changes taking place in the tissues of the organism one would expect that anything that increased such changes would lead to an increased production of bodily temperature. As the previous experiments showed that when sugar is artificially introduced into the circulation, it is to a great extent eliminated from the body as carbonic acid by the lungs in the space of a few hours, this fact pointing to an active oxidation having occurred, it made me desirous to ascertain if a concomitant increase in the animal's temperature could be practically demonstrated. In order to ensure exact results it was necessary in conducting the experiments to take several independent factors into account.

For example, as there is at the same time with the continual production of heat a continual loss of heat by the lungs, and skin, the thermometric measurements of the temperature of any part of the body, let them be taken where they will, offer no information as to the absolute amount of bodily heat developed at any given time; but only of the actual heat of that particular portion of the body. It is consequently necessary to divide the body into three temperature zones—a surface, an intermediate, and a central zone, according as the temperature is taken of a part more or less exposed to the loss of heat. At present I will only speak of the relative changes of temperature induced by the artificial injection of sugar, as ascertained in the central zone of the body. For this purpose a long thermometer was employed, so graduated that the one-hundredth part of a degree centigrade could be read, while the bulb remained as high up as possible in the rectum. In order to be as accurate as possible the thermometer was kept in the same position throughout the whole experiment. When fæces happened to be passed there was always a fall of from $0{\cdot}2^{0}$ to $0{\cdot}5^{0}$ C. This was partly due to the thermometer being somewhat extruded during the act of defæcation.

Moreover all the experiments were conducted in a large room in

which the temperature never varied more than 0·5° C. during their performance.

As previously mentioned, the dogs were always carefully bandaged to a cushion, in order to prevent their making any muscular movements which might lead to any accidental increase of temperature and thereby vitiate the value of the results obtained.

Further, while the animals were under observation, they were lightly covered with cloths, so as to hinder any loss of heat that might possibly occur from the exposed abdominal skin; which from being only slightly covered with hair, yields more heat to the atmosphere than when the dog is lying in his natural curled-up position of repose.

It being well known that the mere fixing of a timid dog to a table, without any operation being performed at all, sometimes induces the temperature to rise 1° C., or more degrees, while the contrary may also occur, as shown by the experiments of G. v. Liebig[1] and Horwath[2], who found that the temperature of animals, kept fixed to a table without any operative interference whatever, sometimes falls as much as 2° C. in a few hours, an interval of twenty minutes was allowed to elapse after fixing the dogs to the table and making the other necessary preparations before beginning the temperature readings. The influence of the nervous system *per se* on the animal's heat was thus reduced as much as possible to a minimum.

Before citing the experiments it may be well to note the following facts:—

1st. The sugar and saline solutions employed were always injected at 39° C., so as not to affect the temperature of the animal.

2nd. As the mere introduction of sugar solution into the circulation invariably increases the frequency of the respiration, and dogs cool themselves principally by their lungs, it is to be noted that this increase in the breathing would of course tend to reduce the temperature of the animal's body and not to increase it.

3rd. As the injection of a sugar solution, as previously stated, induces a rise in the blood-pressure (estimated by Ludwig's kymograph) and at the same time an increase in the quantity of the liquid in the blood—liquid being, as before stated, withdrawn from the tissues into the circulation. This would also tend to reduce the temperature.

These various sources of error were taken into account in making

[1] G. v. Liebig. "Ueber die Temperaturunterschiede des venösen und arteriellen Blutes." *Diss.* Giessen, 1853.

[2] Horwath. *Cent. f. d. med. Wissen.* p. 546, 1870.

the experiments, as well as while considering the conclusions which might be drawn from the results obtained from them.

As regards the construction of the following charts it may be mentioned :—

That the temperatures, which are indicated in black, are in most cases given to 0·02 of a degree, and that the readings were taken every five minutes.

The amounts of oxygen absorbed are indicated in red; and the quantities of carbonic acid eliminated in blue.

The time is noted along the top line of the charts.

The periods during which the respiratory changes are estimated are indicated at the bottom. Thus, ⊏⊏⊏⊏⊐.

The period during which the sugar solutions were injected by ▬.

CHART I. See Plates III. IV. V.

Experiment 3.

Sugar injected. Its elimination by the kidneys being interrupted. No muscular spasms or coma.

As will be observed in Chart I. the temperature slowly but steadily fell up till the time when the warm (39° C.) saline solution containing sugar was injected into the jugular vein. Then there was an immediate rise from 37·20° to 37·38° C. (= 0·18° C.) speedily followed by a fall, during the injecting of the sugar of from 37·38° to 36·72° C. (= 0·68° C.). Next there was a temporary rise from 36·72 to 37·02° (= 0·30° C.) again followed by a gradual fall to almost as low as the lowest point reached, viz. 36·76°. The rise and fall having both lasted forty minutes. During the next hour a steady rise took place to 38·74° (= 2·00° C.), while again there was a twenty minutes' fall. Followed in fifteen minutes by a rise to 38·80° C., which was 0·06° C. above the last highest point. This was followed by a fall of from 38·80° to 38·14° (= 0·66° C.) in twenty-five minutes. There now occurred a marked rise in the next fifty-five minutes, to 39·62° (= 1·49° C.). This was followed by an abrupt fall of over 1·0° C.; probably due to the asphyxia which occurred from there not being sufficient barium solution in the apparatus to absorb all the carbonic acid eliminated by the lungs during the respiratory period *d*, Table IV., as was previously stated.

As artificial respiration had to be performed there was no further reading of the thermometer from 6.40 until 7 p.m.. The fall that had

occurred from the asphyxia supervening was followed by a rise to 38·42° C., which it reached at 7.40 p.m. Then the temperature once more slightly fell and remained at 38·31° C., that being 0·3° C. higher than it was at the commencement of the experiment, before the sugar was injected. At this point it remained until 8.40 p.m. when the dog was killed.

The carbonic acid eliminated, in spite of less oxygen being absorbed, as is seen, increased after the injection of the sugar. In the respiratory periods *c* and *d* (see Table IV.) the carbonic acid however progressively decreased. The oxygen absorbed decreasing still more markedly; while during the respiratory period *e*, the carbonic acid eliminated by the lungs rose somewhat the oxygen absorbed rose at the same time in a still greater degree. This was probably due to the sugar having been to a great extent oxidised into carbonic acid and eliminated by the lungs. It is thus seen that the principal rise of temperature did not correspond with the greatest elimination of carbonic acid, but actually occurred nearly an hour after it.

CHART II.

Experiment 9.

Sugar injected. Its elimination by the kidneys being interrupted. Followed an hour after the injection by coma; which lasted until the dog was killed.

In the above it will be seen that in the first fifteen minutes the temperature fell from 37·6° to 36·8° C. During the hour previous to the injection of the sugar solution the temperature had varied from 36·8° to 37·0° C. Immediately after the commencement of the injection there was a slight rise of 0·08° C. which lasted ten minutes. It then fell somewhat but this rise and fall were too slight to be indicated in the chart; which is only divided so as to show a change of 0·2° C. Towards the end of the injection the temperature rose to 37·4° (= 0·45° C.), after which it kept during an hour and a-half almost at the same point as it had been before it; namely 36·8° C. The dog then slowly became comatose and the temperature steadily fell from 36·8° C. at 11. 50 a.m. until it reached 31·2° C. at 5.55 p.m.; that is in 6 hours. There was an exceptional rise at 2.10 p.m. but this may be allowed to pass unnoticed, as like the previous quicker fall (at 1.55 p.m.) it can be accounted for by the passage of fæces.

The carbonic acid eliminated steadily diminished in quantity during

each successive respiratory period. The oxygen absorbed did exactly the same, only to a more marked degree.

CHART III.

Experiment 4.

Sugar injected. Its elimination by the kidneys being interrupted. Followed by profound coma.

This is an exceptionally interesting case, from the dog's temperature falling in the space of $12\frac{1}{2}$ hours to the extent of 10 degrees centigrade.

During the hour prior to the sugar injection the temperature fell from 39·0 to 37·6 C. And although at the commencement of the injection of the sugar solution, there was a temporary rise of 0·05° C., it continued to fall until towards the end of the injection, when there was again a rise from 35·82° to 36·06° (= 0·14° C.). This lasted fifteen minutes. The temperature then returned to 35·8° C., at which point it remained almost constant during an hour. Then it began again to fall and continued to fall almost regularly until it reached 28·62° C. At which point the dog was killed.

The fall before the sugar injection, which may perhaps be explained by fear, probably corresponds to the fall of bodily temperature, pointed out by Horwath as occurring in rabbits. But the steady fall after 1 p.m. appeared to be entirely due to the comatose state which supervened, and it continued up to the time the animal was killed.

It is here seen that during the first three hours after the sugar injection both the carbonic acid eliminated and the oxygen absorbed were increased. In spite of this increase in the amount of carbonic acid eliminated there was however only a slight rise in the temperature during the respiratory period *b* (Table VI.), and when the carbonic acid eliminated still further increased during the third hour (respiratory period *c*) there was a marked fall in the temperature. In the last respiratory period *e* the carbonic acid eliminated was more than the oxygen absorbed during the same period, and both were very markedly decreased, almost to a quarter of the normal standard.

The possibility that the great fall in the temperature might have some connection with the retention of the urinary ingredients in the blood, after the ligature of the ureters, and not be entirely due to the nervous symptoms produced by the sugar is at once seen to be negatived by the following chart.

CHART IV.

Experiment 6.

Effects of the injection of a 0·75 p.c. solution of chloride of sodium, coupled with a previous ligaturing of the ureters.

The above (Chart IV.) shows that the effects of ligaturing the ureters and injecting a normal saline solution causes only a slight rise in the temperature, together with (at first) a rise in the elimination of carbonic acid, but with no increase in the oxygen absorbed.

Thus in the forty-five minutes before the injection, the temperature fluctuated between 36·92° and 37·46° C. Whereas immediately after the saline solution was introduced into the jugular vein it rose within the space of twenty-five minutes from 37·32° to 37·54° C., when the temperature fell to 37·18° C. It then steadily rose during the next two hours in almost a continuous line to 38·46° (*i.e.* 1·28° C.). It now fell with some undulations during the next $3\frac{1}{2}$ hours. While it kept a pretty steady course for the last four hours, being 37·76° C. 12 hours after the introduction of the saline injection.

The oxygen absorbed shows a sudden drop during the first hour, at 1.20 p.m. Just as the temperature is rising it is again somewhat increased; after which there is merely a slight tendency to fall. While the carbonic acid at first increases; but is followed by a tendency to fall in the same ratio as the oxygen.

CHART V.

Experiment 5.

Sugar injected without its elimination by the kidneys being interfered with. No nervous symptoms occurring.

In this case (Chart V.) the temperature steadily fell in the first 65 minutes from 37·60° to 36·02° C., *i.e.* 0·58° C. On the sugar solution being injected it continued falling until 70 minutes later, when it reached 34·74° C. It then rose in the following fifteen minutes 0·08° C., after which it again fell even lower than before, reaching 34·60° C. It now steadily rose 2·6° C., reaching 37·20° C. in the next 5 hours, when again there was a fall in 50 minutes of 0·4° C., followed in nine hours after the injection of the sugar by a rise to 37·54° C.

Here with the great fall of temperature immediately before and after the sugar injection there is a diminution in the carbonic acid eliminated and the oxygen absorbed. This is followed by a rise in

both, before the temperature rose, and again a fall, at the time the temperature was high.

CHART VI.

Experiment 7.

Sugar injected without its elimination by the kidneys being interfered with. Followed by no nervous symptoms.

The temperature steadily fell (Chart VI.) in this case, from 36·60° to 34·60° C., as in the preceding one, except at the commencement of the injection when it rose 0·04° C., reaching the lowest point 40 minutes after the sugar solution was injected. There was then a rise during five minutes of 0·38° C., from 34·60° to 34·96° C., when it again fell in 45 minutes 0·46° to 34·50° C. We have then in the next four hours an almost continuous rise of 3·10° to 37·60° C., followed by a fall of 0·5° C. in half-an-hour. And again a rise to 37·70° C.; which point it reached $6\frac{1}{2}$ hours after the sugar was injected. It now fell in two hours nearly a degree, when it remained at a level of 36·72° C. for an hour.

These changes in temperature are almost the same as those seen in Chart V., whereas the gaseous changes are different. For here it is seen that the carbonic acid elimination steadily increased as the temperature rose, and the oxygen absorbed to a certain extent did the same.

CHART VII.

Experiment 8.

Sugar injected without the renal excretion being interfered with. No apparent coma.

It is here seen (Chart VII.) that the temperature fell before the injection of the sugar from 38·45 to 37·90° C. (= 0·55° C.). On the sugar being injected there was a rise of 0·4° C., during 15 minutes. This was followed by an uninterrupted fall of animal heat during the next 6 hours to the extent of 7·32° C. when it had reached 30·62° C. The dog was then killed.

The carbonic acid eliminated also fell; and the oxygen absorbed did so in a more marked manner.

As in this case, there was no coma, it cannot be explained like the cases referred to in Charts II. and III. No explanation is found for it unless it be that some dogs are extra timid, and consequently show in an exaggerated manner the fall of temperature caused by binding an animal to a table, as already mentioned was observed by Horwath.

Conclusions.

On looking over the results obtained from the foregoing experiments one finds they may be briefly summed up as follows :—

Grape-sugar injected into the circulation of dogs, when its elimination by the kidneys is interrupted, causes an increase in the respiratory quotient.

That the respiratory quotient begins to rise during the first and steadily increases during each successive hour, reaching its maximum about the fifth. After which it returns to what it was before the sugar was introduced into the circulation.

When coma follows as a result of sugar injection the respiratory quotient goes on increasing, until it may reach in the space of ten hours as much as 1·07 (Table VI.).

When the elimination of the injected sugar by the kidneys is not interfered with, the rise in the respiratory quotient continues to increase not only up to but even after the ninth hour. But it is much less marked than when the elimination of the sugar by the kidneys is interrupted.

As a molecule of sugar contains enough oxygen to saturate the hydrogen present in it, in order to oxidise the whole of the sugar molecule into carbonic acid and water, each atom of carbon requires two atoms (one molecule) of oxygen to form one molecule of carbonic acid, it is seen that in the above experiments the increase in the oxygen absorbed was not sufficient to oxidise all the carbon. Consequently one is forced to believe that a certain amount of carbon and hydrogen had been retained in the organism, most probably to form some other carbohydrate containing less oxygen than the sugar molecule.

As regards the temperature changes, although there is still more difficulty in drawing definite conclusions, it may be noted that the introduction of sugar into the circulation seems to cause an increase in the animal heat of about 1·5° C. when no nervous symptoms arise to complicate the results.

If coma supervenes on account of sugar injection the temperature steadily falls. In one case, Chart III., it fell as much as 10·4° C. in the space of twelve and a-half hours. Further we have in Chart VII. an exceptional case in which the temperature fell in spite of no recognisable nervous symptoms supervening.

The temperature does not rise and fall with the increase and decrease in the oxygen absorbed as one would expect, but runs a

perfectly independent course. I do not with our present knowledge see any means of explaining this circumstance, unless by imagining that as sugar can produce such severe nervous disturbances as suffice to induce muscular spasms and coma, it also acts in a special way on the heat-regulating nerve centres.

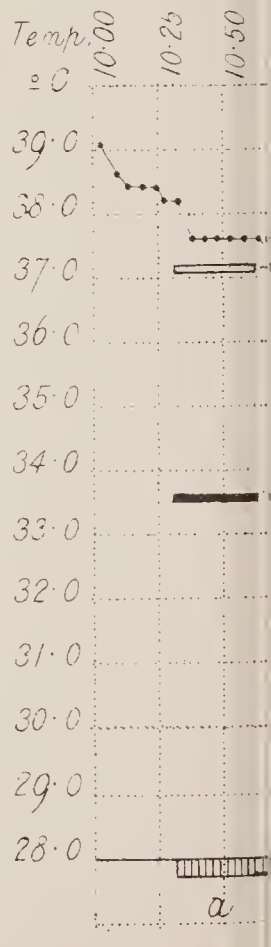
Neither the temperature nor the respiratory changes can, any more than the nervous symptoms, be put down to the mere retention of urinary ingredients in the blood. For as shown in Table VII. and by Chart IV. no nervous symptoms are caused by the ligature of the ureters.

The injection of a physiological saline solution, on the other hand, only causes a rise in the respiratory quotient; which reaches its maximum in the first, and has begun to fall before the third hour.

The temperature increase is less marked, and of far shorter duration than what is produced by sugar injections.

Temp. °C.
1·30
1·55
2·20
2·45
3·10
3·35
4·00
4·25
4·50
5·15
5·40
6·05
6·30
6·55
7·20
7·45
8·10
8·35
9·00
c.c.
39·60
·50
·40
·30
·20
·10
39·00
·90
·80
·70
·60
·50
·40
·30
·20
·10
38·00
·90
·80
·70
·60
·50
·40
·30
·20
·10
37·00
·90
·80
36·70
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
a
b
c
d
e

Chart I.


Temp. °C
10·00
10·25
10·50
39·0
38·0
37·0
36·0
35·0
34·0
33·0
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31·0
30·0
29·0
28·0
a

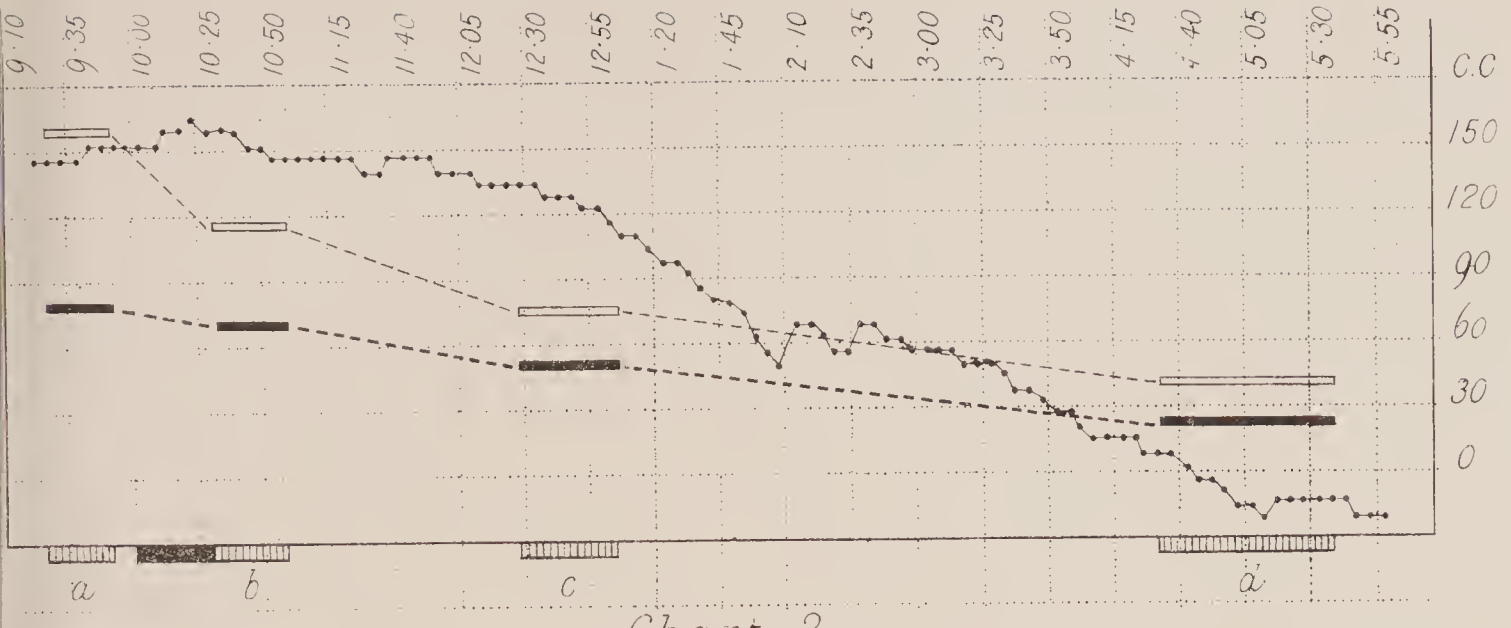

Chart 2.

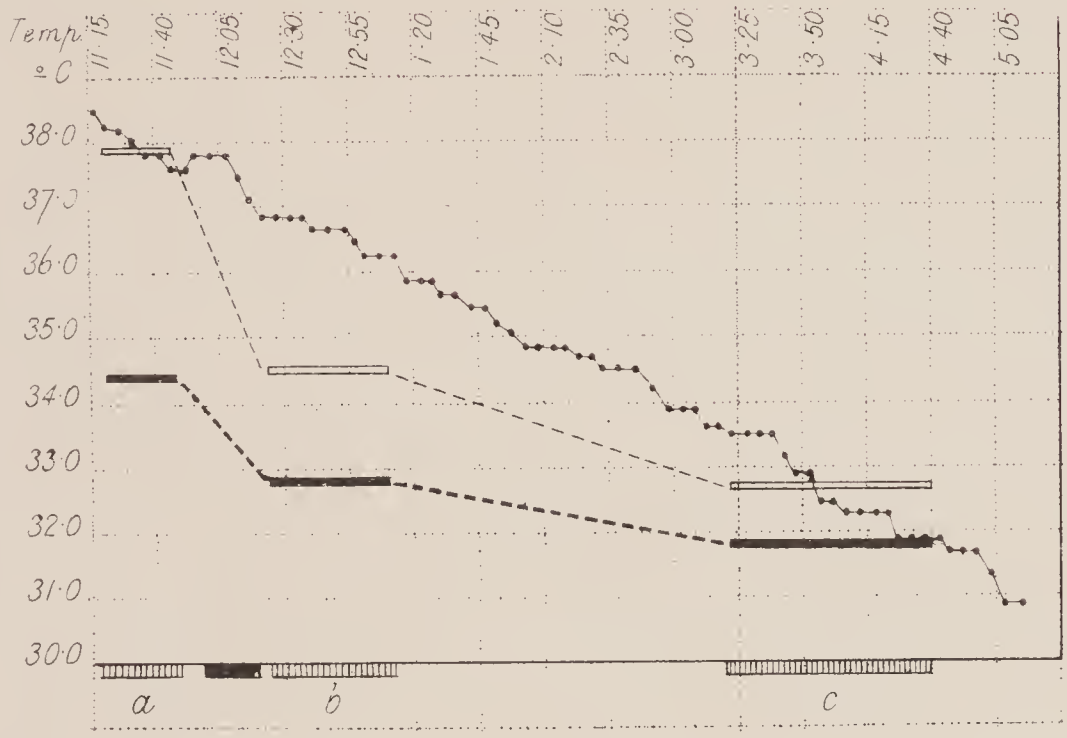

Chart 7.

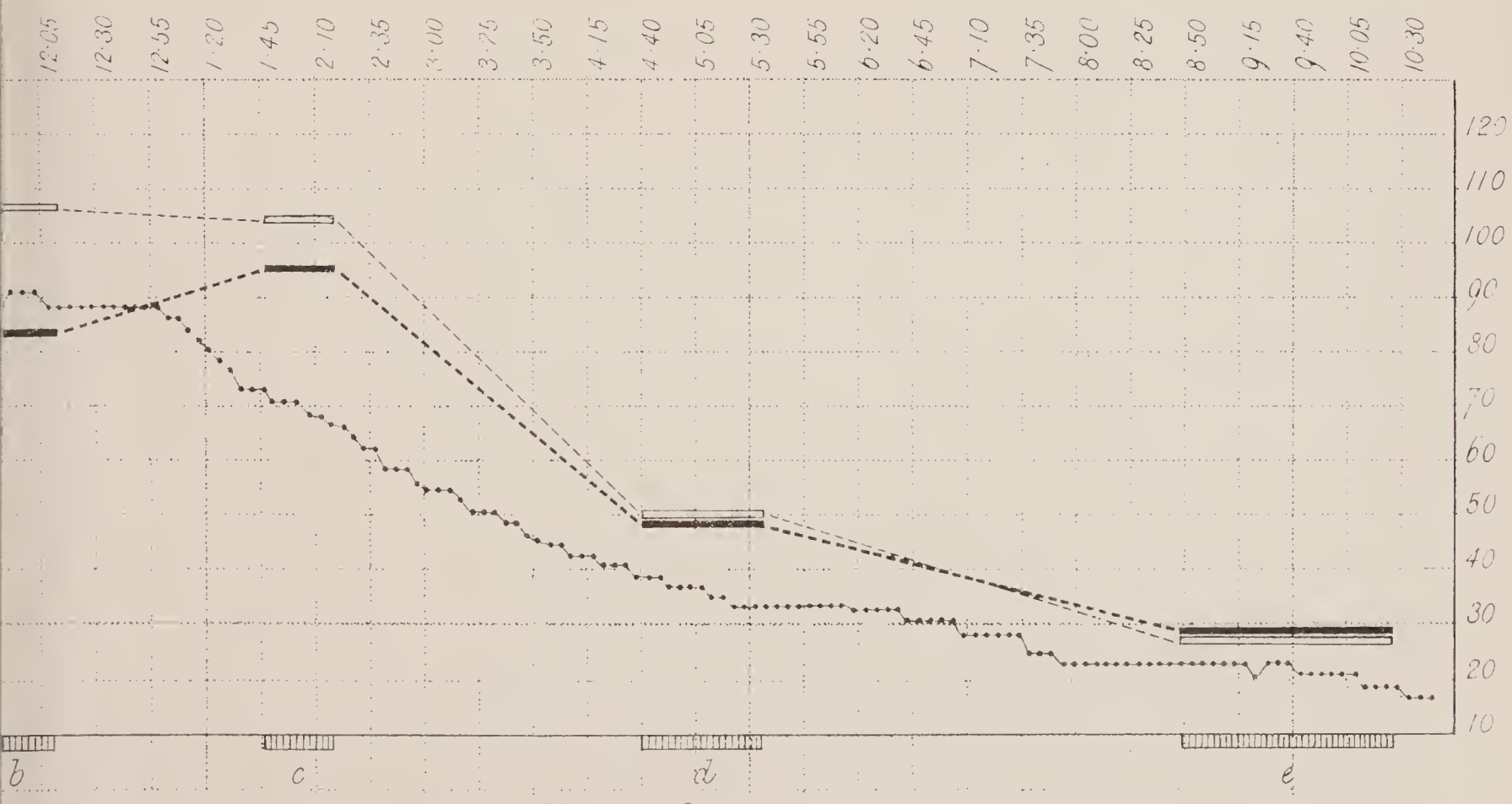

Chart 3.

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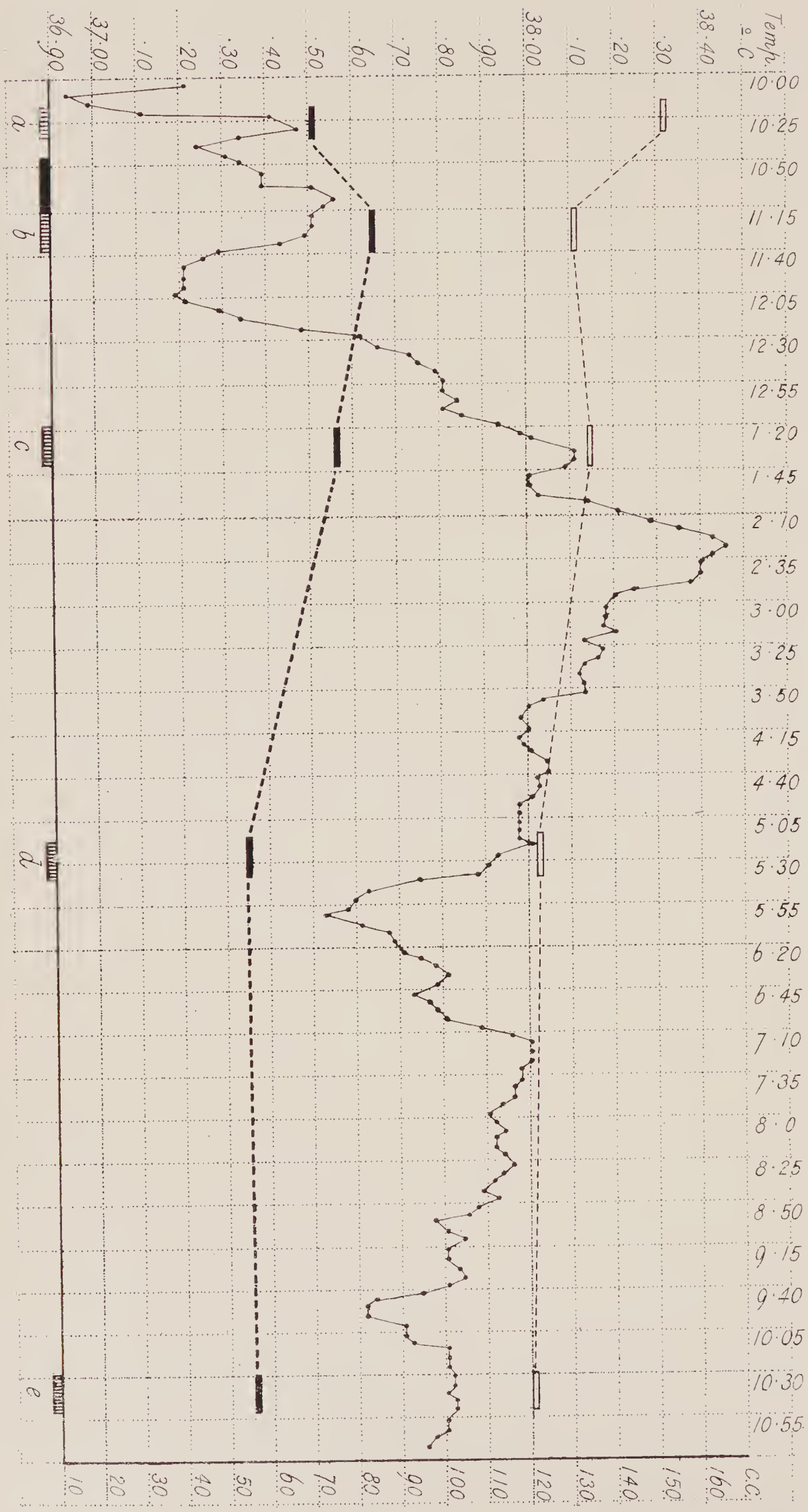
Temp. ° C
36·90
37·00
·10
·20
·30
·40
·50
·60
·70
·80
·90
38·00
·10
·20
·30
38·40
a
b
c
d
e
10·00
10·25
10·50
11·15
11·40
12·05
12·30
12·55
1·20
1·45
2·10
2·35
3·00
3·25
3·50
4·15
4·40
5·05
5·30
5·55
6·20
6·45
7·10
7·35
8·0
8·25
8·50
9·15
9·40
10·05
10·30
10·55
10
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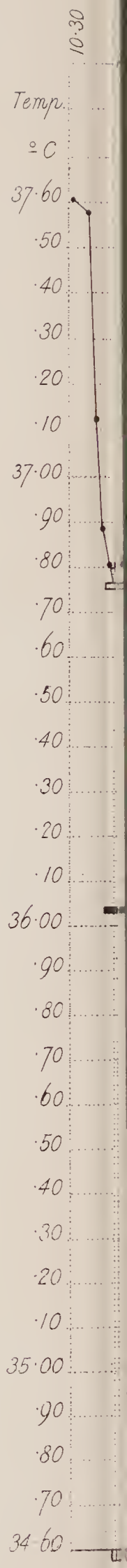
50
60
70
80
90
100
110
120
130
140
150
160
C.C.

Chart 4.


10·30
Temp.
° C
37·60
·50
·40
·30
·20
·10
37·00
·90
·80
·70
·60
·50
·40
·30
·20
·10
36·00
·90
·80
·70
34·60

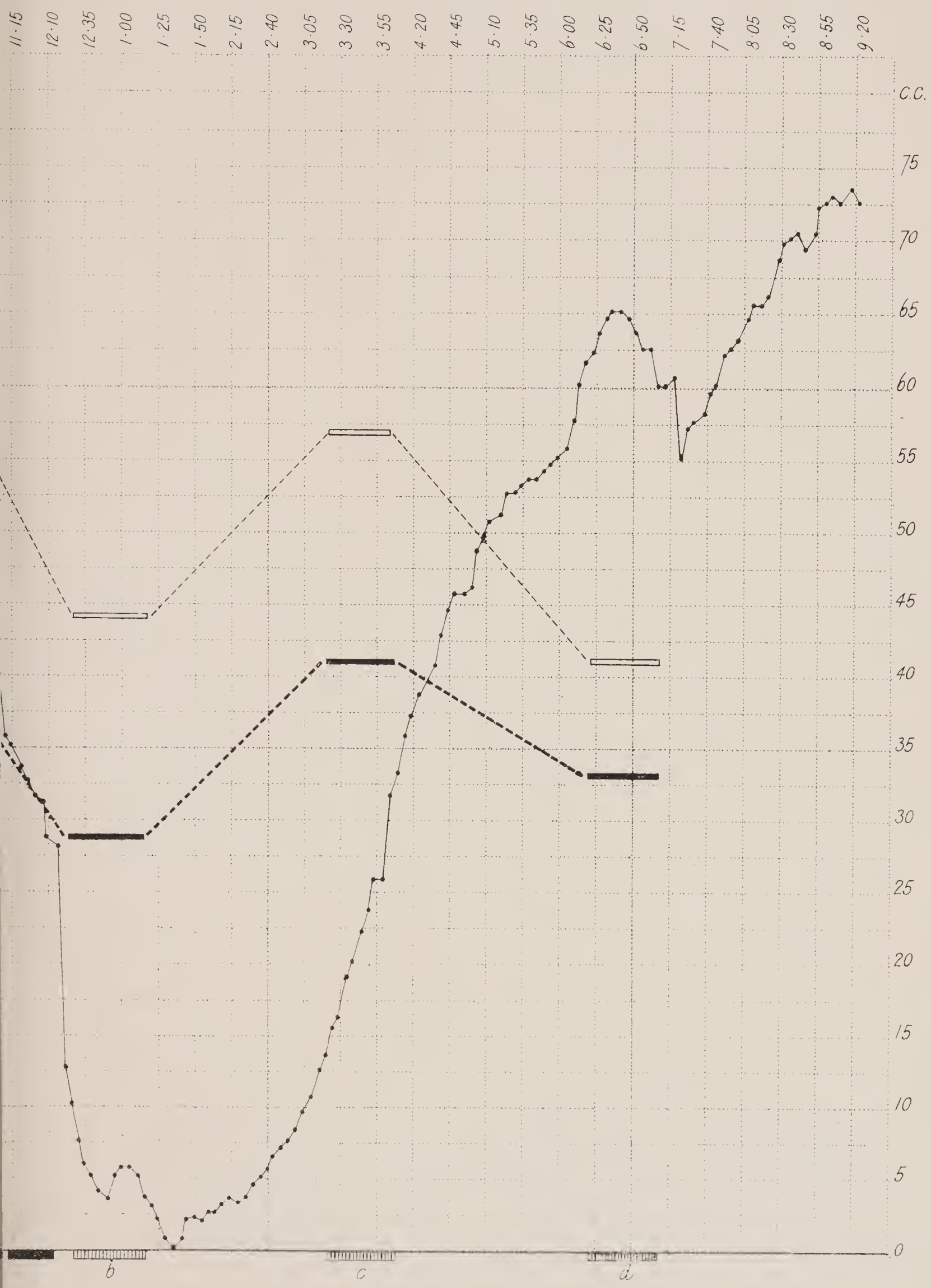


Chart 5.

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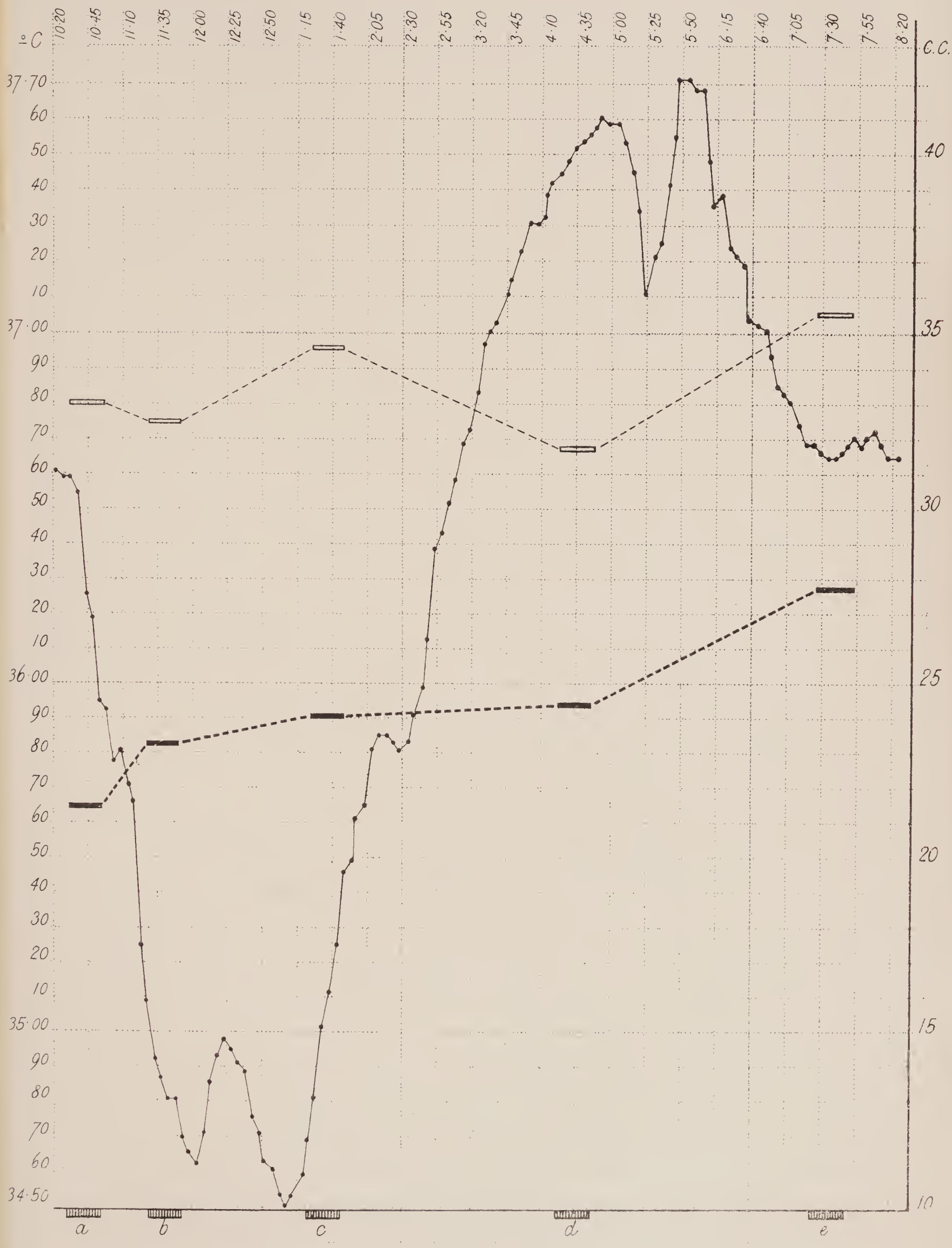

Chart c

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THE TREATMENT OF MYXŒDEMA AND CRETINISM,

Being a Review of the Treatment of these Diseases with the Thyroid Gland, with a Table of 100 Published Cases.

BY

CECIL F. BEADLES, M.R.C.S., L.R.C.P.,

Assistant Medical Officer, Colney Hatch Asylum.

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The Treatment of Myxœdema and Cretinism,

Being a Review of the Treatment of these Diseases with the Thyroid Gland, with a Table of 100 *Published Cases.**

By CECIL F. BEADLES, M.R.C.S., L.R.C.P.,

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Introductory.

I propose in the following paper to review briefly the treatment that has recently been made use of in myxœdema, and compare the several ways in which it has been carried out, after a few preliminary remarks on the pre-thyroid methods.

First let me note that myxœdema, although not common, is now known not to be so rare a disease as was supposed only a few years back. During the past five years, that is to say from the year 1888, when the profession was more generally awakened to the existence of this disease by the Clinical Society's report, up to the present time a careful search reveals just 200 distinct cases† referred to in the various medical

* The most important discussions that have yet taken place are those at Nottingham in July, 1892 (in the early days of the new thyroid treatment), and Edinburgh, February 15th and 16th, 1893. To the reports of these I would direct your attention. I understand that at the annual meeting of the British Medical Association, at Newcastle, in August next, Prof. Horsley has promised to open a discussion on "The Thyroid."

† These include 40 cases referred to at the Edinburgh Med.-Chir. Soc. on February 15th and 16th, 1893, but not the 50 cases which were then mentioned as known to exist about the neighbourhoods of Edinburgh and Dundee.

journals of this country. But the vast majority of cases go unrecorded, for until within the last eighteen months cases were seldom reported unless there was something of particular interest in the symptoms of the case, or some point in the pathology of the disease that was thought worthy of notice.

The Older or pre-Thyroid Methods of Treatment.

From the time Sir William Gull* in 1873 first called attention to the disease now known under the name of myxœdema,† up to July, 1891, when Dr. George Murray read his paper in the Section of Therapeutics of the British Medical Association, at Bournemouth, entitled "Note on the Treatment of Myxœdema by Hypodermic Injections of an Extract of the Thyroid Gland of a Sheep," no treatment was known that could be said to have anything but the slightest influence on this slowly progressive disease, much less cure it. Since Dr. Murray's valuable suggestion, however, I think we may say that we now have in our possession a substance which can produce a greater change in persons suffering from myxœdema than is the case with any single drug or any other known disease.

During the time above-mentioned most of the preparations in the pharmacopœia, as well as others not contained therein, had been tried with a singularly unfavourable result. There was only one drug known that appeared to exercise any notable influence for the better. This was jaborandi.

Of the 65 out of the 109 cases of myxœdema reported on by the Committee of the Clinical Society‡ in which the form of treatment adopted was specified, this was the only drug mentioned that seemed to be followed by a slight improvement. It was made use of in eighteen of the cases. This result was the same as that which has since been observed, and the result was similar in a patient I had under my care in Colney Hatch Asylum§ in the early part of 1892, where she had been an inmate over seven years. Although a slight improvement at

* "On a Cretinoid State supervening in Adult Life in Women," Clin. Soc. of London, 1873.

† "Ord. Medico-Chir. Trans.," Vol. lxi., p. 57, 1877.

‡ "Report of a Committee of the Clinical Society of London to investigate the subject of Myxœdema," 1888.

§ Case reported in "The Journal of Path. and Bact.," No. 2, 1892.

times appeared to follow the administration of jaborandi, it was only very transitory, with but a slight noticeable change either in the bodily or mental symptoms, and the patient rapidly relapsed into her former condition.

Myxœdema is naturally a very chronic disease, in which periods of abatement are wont to occur, and, as is well known, myxœdematous patients under no special treatment vary greatly from time to time, but especially so with change of temperature and the season of the year; but although they feel in better health and are more active when the weather is warm, they never lose the characteristic facial aspect, although it may to a slight degree diminish. I have never heard of a patient who has so far recovered that it has been impossible to diagnose the case as one of myxœdema. They are always worse in the winter months, and it is then that death almost invariably takes place. Some of the improvement that has been said to occur after the use of jaborandi may therefore depend on the patient's surroundings, and it should be stated in which months this has taken place—a point which has not always been noted, and has, therefore, tended to somewhat mislead as to the benefit derived from this medicine.

Dr William Ord* at one time went so far as to state that in a few cases "under the prolonged use of jaborandi the signs of myxœdema have almost disappeared." But even this is by no means the rule, and only the other day Dr. Ord remarked at the Clinical Society† that "two years ago the disease was regarded as incurable."

The Committee appointed by the Clinical Society in their classical work on myxœdema already referred to, in their general summary of treatment, say :—"The use of tonics, particularly of iron, quinine, and hypophosphites (meeting the obvious debility belonging to the disease) has been adopted with a certain amount of temporary success. Having regard to the defective action of the skin, Jaborandi and pilocarpin have in many cases been administered, and, when administered over long periods, have appeared to exercise much beneficial influence. Nitro-glycerine has been used in a very limited number of cases with fairly good results. An important element in the treatment is the maintenance of warmth in the surrounding atmosphere, and the regular removal of patients during the winter to southern climates has appeared to mitigate

* Quain's "Dictionary of Medicine," 1883, p. 1016.
† "Brit. Med. Journ.," February 4th, 1893, p. 252.

their sufferings and to prolong their tenure of life."* On another page† they enter more fully into the results reported of individual drugs.

Other drugs appear to be of even less value, and the same remarks apply as those just made with regard to jaborandi. Of the drugs which have had special attention called to them and been stated at various times to have been used beneficially may be mentioned nux vomica, strychnia, arsenic and iron, and nitro-glycerine, by the use of which drugs, when combined with careful diet, baths, and massage, Sir Andrew Clark "regards the disease as fairly curable."‡ This is a vague term, and few would hold that there is even a "temporary cure" by these means.§ There are few illustrations on record. Dr. McCall Anderson, of Glasgow, has lately published a case ‖ of a female, 20 years of age, with myxœdema of one year duration. The treatment consisted of taking arsenic and strychnine internally with a shampoo daily for half-an-hour, and an occasional vapour bath, in addition to which every now and then she had a subcutaneous injection of pilocarpine, gr. $\frac{1}{4}$, and a hot electric bath for half-an-hour at a time. A change for the better commenced after ten days, and in three months' time "great improvement was manifest." This, of course was an early case; the mind was not impaired. In another case, of longer duration, which he publishes at the same time, similar treatment produced no result after continuation for two months; it was then combined with the administration of thyroid juice, and was followed by marked improvement. I shall, however, refer to this case again.

Dr. A. Morison, at a meeting of the Pathological Society on October 18, said "he had seen a great benefit follow systematic

* "Myxœdema Report," p. 34.

† This is as follows:—"Jaborandi in 12 and pilocarpin in six. Of these 18, 11 improved. In three improvement was great, and in one of these hot-air baths were also used. In five no improvement; in two results not stated. Nitro-glycerine in three. Marked temporary improvement in one, slight improvement in one, no effect in one. Iron, quinine, and sulphur baths caused almost entire disappearance of œdema in one. Iodide of potassium in large doses temporarily relieved occipital headache in one. Induced current in two. Improvement in one. Galvanism to the spine probably of use in one. Iron beneficial in four, but in a much larger proportion no good resulted. Strychnia or nux vomica in 10. Improvement in two. Quinine, hydrobromic acid, phosphorus, cod-liver oil, cold baths, milk diet, and 'tonics' apparently useless." The above are extracted from 65 answers received. See page 22 of report.

‡ Quain's "Dictionary of Medicine," 1883.

§ Dr. Affleck ("Edin. Med. Jour.," May, 1893, p. 1050) has, however, known great improvement to follow this treatment.

‖ "The Practitioner," January, 1893.

massage; the patient improved for a time, but ultimately the massage lost its apparent effect and a fatal result ensued.* Other observers have noted precisely the same fact.

Dr. William Dyson, in recording a case of myxœdema in a male who was under his care at the Sheffield General Infirmary,† writes, "On the whole the drug treatment did not appear to do much good; I was inclined to attribute this general improvement to the warmth, excellent nursing, and good wholesome food which he received." A photograph reproduced, which was taken when he was at his best, shows, however, an undoubted well-marked case of myxœdema. With this remark of Dr. Dyson many will agree.

Dr. Hector Mackenzie, lately in a lecture on the recent advances in the treatment of myxœdema, when speaking of a certain case that he has since treated by thyroid extract, said: "During the two years and a half we had been watching the patient the disease had been slowly, but steadily, progressing. Whether our treatment by jaborandi, tonics, rest in bed, massage, and the other means we had employed had prevented a more rapid progress we cannot say. Certainly, she had been temporarily benefited a little by her two admissions, and she herself had some faith in the efficacy of the medicines prescribed for her."‡

Dr. Hermon Gordinier read a paper last year before the Medical Society of New York, in which he said of a female with myxœdema of two years' duration, "The patient has been under my care for over a year, and I can see but little improvement in her condition. She thought at one time that pilocarpine did her good."§

The uselessness of a "tonic treatment" has been shown again and again. Dr. Benson|| records a case of eight years' duration in which this treatment was persisted in for five months "without any effects." The thyroid extract was given by the mouth, and in less than a month she became a "new creature."

We must conclude, therefore, that by such treatment little could be hoped for beyond producing a very temporary benefit by improving the appetite and increasing the action of the skin.

* "Lancet," October 22, 1892.
† "Sheffield Medical Journal," No. 1, October, 1892.
‡ "Lancet," January 21, 1893.
§ "Medical Reprints," September 15, 1892. "Report of Two Cases of Myxœdema with one Autopsy."
|| "Brit. Med. Journ.," April 15, 1893, p. 795.

The Treatment of Myxœdema by Thyroid Grafting.

So much for the older methods of treatment. I now pass on to the more modern form, viz., the treatment of myxœdema by means of the thyroid gland.

First, I will deal with the subject in its primary or surgical aspect, viz., thyroid grafting, and afterwards with the modifications and improvements that have since been introduced, by which the treatment has been simplified, rendered more efficient, and at the same time taken out of the hands of the surgeon and given into those of a larger class of men—the physicians and general practitioners.

It was in February, 1890, that Prof. Victor Horsley suggested the transplantation of the thyroid of a healthy sheep into persons affected with myxœdema, with the view to arresting the progress of the disease, basing his arguments on the experiments of Schiff, Eiselsberg, and his own.* These experiments went to prove that, when the myxœdematous process (cachexia strumipriva) developed in an animal deprived of its thyroid gland, the animal could be kept alive and in good health by the transplantation of the same gland from another healthy animal.

Cases are often recorded in the medical journals immediately after an operation or at the commencement of a new form of treatment, and we hear no more about them. Some of these are exceedingly interesting, and we should like to know how the case progressed and what was the final result of the treatment recommended. A case in point is that of thyroid grafting for myxœdema. Now that the subject of myxœdema is attracting so much attention, it would be interesting to know what has become of those patients who have been treated by this method, whether they show any permanent improvement, and how this mode of treatment compares with that of the subcutaneous injection and ingestion of the thyroid extract in this disease.

With this object I have collected together all the cases of which I know, and, where possible, have obtained further information concerning them. Let us see what have been the results so far.

M. Lannelongue, of Paris,† appears to have been the first

* "Note on a Possible Means of Arresting the Progress of Myxœdema, Cachexia Strumipriva, and Allied Diseases." "Brit. Med. Journ.," Feb. 8, 1890, p. 287.

† "Lancet," March 22, 1890, p. 665.

to carry out the operation. He reported his case to the Biological Society on March 7th, 1890, immediately after the patient had recovered from the operation and before any change in the patient's condition had occurred. No further information concerning this patient has been reported in the English journals, and we do not know if any improvement followed the operation. On September 3rd, 1890, M. Walther* performed a similar operation on a woman, 40 years of age, and reported the case to the Medical Society of Paris, the following November: slight improvement with less characteristic appearance of myxœdema was noted. Here again we are left in ignorance as to a later result. In the meantime Drs. Battencourt and Serrano, of Lisbon, reported on the subject of thyroid grafting for myxœdema.† Their case is briefly as follows:—A female, æt. 36, had myxœdema for several years with apparent absence of the thyroid. These observers introduced into the subcutaneous tissue of the inframammary region on each side the half of a thyroid gland of a sheep. An immediate amelioration was produced, which was first marked by an elevation of the temperature. The red blood corpuscles rapidly increased in one month from 2,442,000 to 4,447,000. The patient's movements became more easy, her speech less affected, and perspiration returned. The œdema went down, and her weight diminished from 239 lbs. to 227¾ lbs. Menstruation now lasted only four days, whereas, previously, it was many weeks. It is to be noted that Battencourt and Serrano state, "The fact that amelioration commenced so soon seems to indicate to us that the thyroid tissue was absorbed."‡ This account, which appears to have been written about a month after the operation, is the latest to hand.

Mr. Hurry Fenwick§ first performed the operation in this country. It was on a woman, and was carried out at the request of Dr. Sansom. No improvement followed, for "the disease was too advanced to admit of any satisfactory inference being drawn as to the efficacy of the method." The case was fatal on the fifth day.

On April 2, 1891, Dr. W. J. Collins transplanted the thyroid gland of a sheep into a patient at the Temperance Hospital at the suggestion of Dr. Ridge.‖ The patient was a woman

* "Lancet," Nov. 29, 1890, p. 1192.

† "La Semaine Médicale," Aug. 13, 1890.

‡ For the translation notes of this case, and from which the above is taken, I am indebted to my friend Dr. Boyce.

§ "Lancet," May 2, 1891, p. 1003; also "Brit. Med. Journ.," Oct. 10, 1891.

‖ "The Medical Pioneer," Oct., 1892, and "Lancet," May 2, 1891, p. 1003.

aged 34. The symptoms, which commenced two years back, do not appear to have been advanced. Dr. Collins' latest remark on the case was in September, 1892. He says: "She pronounces herself in good health, is cheerful. Those who watched the patient most closely insist upon mental improvement having taken place, and there are not wanting more material points in which involuntary misconception is less probable."

Of the two remaining cases of thyroid grafting, that of Dr. Thomas Harris and Mr G. A. Wright was reported fully in the "Lancet."* The patient, a woman aged 48, who had shown signs of the disease for nine years, had, on April 4th, 1891, at the Manchester Royal Infirmary, part of the thyroid of a young monkey inserted beneath the breast. The operation was quickly followed by improvement in some respects, but in a few weeks the patient appears to have relapsed completely into her former state. She improved slightly again on returning to the Infirmary, a fact which the authors attribute to hospital diet and surroundings. Her speech remained quite unaffected. In reply to an inquiry as to the condition of the patient more recently, Mr. Wright, on October 18th, 1892, writes as follows: "The myxœdema case has not turned up lately, but when I saw her last she was much the same as before, though she thought herself better. Nothing further has been done so far as I know. My impression was that the stay in hospital improved her a good deal more than the thyroid grafting."

On the 2nd March, 1892, Dr. John Macpherson† showed a patient at a meeting of the Edinburgh Medico-Chirurgical Society on whom he had performed this operation on the 22nd October previously. The patient, who was an inmate of the Stirling District Asylum, was a woman, 39 years of age, with myxœdema of three years' standing. A remarkable mental and physical change followed rapidly on the operation, and appears to have continued for a time. On October 11th, 1892, Dr. Macpherson was good enough to write me: "My patient has quite recently been readmitted into this asylum. When formerly under my care she was melancholic, stuporose, and otherwise manifested the usual mental concomitants of myxœdema. On this occasion she is mildly maniacal, and she presents none of the mental or physical symptoms of myxœdema."

* "Lancet," April 9, 1892, p. 798.
† "Edin. Med. Journ.," May, 1892, and "Lancet,' May 12, 1892, p. 609.

Writing again under date of May 11th, 1893 (just seven months later), he says: "The case is still under my care in this asylum. She is subject to slight recurring attacks of mania and melancholia, the latter, when it occurs, being characterized by mild stupor. Occasionally there appears on her cheeks the characteristic pink flush of myxœdema—the only symptom, if one accepts the mental disturbance as doubtful, of myxœdema. I am quite prepared to observe a relapse in her condition at any time. It suggests to my mind the possibility that there is just sufficient thyroid secretion being produced to prevent pathological symptoms, and that occasionally when the production falls below the necessary requirement of the system the mental symptoms make their appearance."

In this case, in which the myxœdema seems to have been more or less cured, there is raised the question as to the cause of the insanity, and this case would appear to make it the more difficult to explain the reason for the insanity that follows on myxœdema.

In addition to these cases, at a recent meeting of the Clinical Society of London, Dr. Ord said he had tried implantation of the thyroid gland with only temporary success.*

Note.—The operation of thyroid grafting for cretinism is commented on elsewhere. The results of Bircher ("Sammlung klinischen Vorträge," No. 357, 1890) and Kocher, obtained by thyroid grafting on the subjects of cachexia strumapriva, are not here referred to, as they form a slightly different class of cases.

From the above references it will be seen that regarding the ultimate effect of the treatment in the earliest cases, those operated on abroad, we are ignorant, and it is to be hoped that an endeavour will be made to trace them. Excluding Mr. Fenwick's case, there remain four cases of which we know something. Of these, two appear to have been followed by a more or less prolonged period of improvement, the others only very temporary. Of Dr. Macpherson's and Dr. Collins' cases there are points worth noting. In the first the insanity returned within a few months, and concerning the second one can read in Dr. Collins' words that signs of the disease are still present although the disease was never advanced.

On the whole, I think we may conclude, therefore, that at present there appear to be no advantages to be gained by the severer operation of grafting over the minor one of subcu-

* "Lancet," Feb. 4, 1893, p. 248.

taneous injection, or the simple ingestion of the thyroid principle; moreover, we cannot at present point to a collection of cases such as we now have with the latter where the treatment has been followed by such uniform results.

Historical Sketch of Recent Modifications in the Treatment of Myxœdema by Subcutaneous Injection and Ingestion of an Extract, etc., of the Thyroid Gland.

We now come to the more recent suggestion of Dr. George Murray, a pupil of Prof. Victor Horsley. Dr. Murray being struck with the rapid action that was recorded as following the operation of thyroid grafting concluded that this was due to the absorption of the thyroid juice that was still present in the piece of thyroid tissue at the time of implanting, as the interval was too short for the formation of either fresh secretion or new thyroid tissue. Working on this hypothesis, he prepared an extract of the fresh thyroid gland of a sheep by mincing the gland and extracting the principle with glycerine, and injecting this subcutaneously into a patient the subject of well-marked myxœdema. The result was astonishing, and he communicated it to the profession, as already stated, at Bournemouth, in July, 1891.

On the Continent, about the same time, Brown-Séquard and d'Arsonval are said* to have suggested, from the experimental results obtained on animals by Vassale and Gley, the probable utility of thyroid juice in myxœdematous persons if injected hypodermically. But they do not appear to have carried it into practical effect. Bouchard,† later, came to similar conclusions from his own experience.

Murray's paper appeared in the "British Medical Journal,"‡ and the treatment there proposed, of the subcutaneous injection of a glycerine extract of the thyroid gland of some animal, has since been carried out in a large number of cases, and the results obtained have been almost invariably as satisfactory and wonderful as those first recorded, in many cases even more so.

Up to the present time (May 18th), so far as I have been able to discover, there have been 100 cases published in which this treatment, or some modification of it, has been tried. About 40 of these were actually treated by the subcutaneous

* "Lancet," Jan. 21, 1893, p. 124.

† "Brit. Med. Journ." (Epitome), Nov. 12, 1892, and "Arch. Gén. de Méd.," Oct., 1892.

‡ "Note on the Treatment of Myxœdema by Hypodermic Injections of an Extract of the Thyroid Gland of a Sheep." "Brit. Med. Journ.," Oct. 10, 1891.

injection of an extract in all respects similar to that used by Murray.*

A large number of the cases appeared originally in "The British Medical Journal," and the majority of those elsewhere reported, may be found referred to in that journal.† With the exception of two cases they have all been followed by a remarkable improvement in the condition of the patients. The two exceptions were those referred to by Dr. Michell Clarke, at the meeting of the British Medical Association at Nottingham.‡ No details are given, but it is said that "no change resulted from the injections," a fact exceedingly strange when we consider that every other observer who has carried out this treatment has obtained so marked an alteration in the appearance of the patients when the subject of myxœdema. One, therefore, cannot help thinking that some discrepancy must have occurred in the diagnoses or mode of treatment adopted by Dr. Clarke.

Murray's method was a much simpler one than that of implantation, and the risks of a large operation were done away with; at the same time the immediate results were more satisfactory, and the remote were equally good or better.

The next real advance made in the treatment was that proposed by Dr. Hector Mackenzie.§ On July 27th, 1892, being unable at the time to obtain the extract for injection, he commenced to feed a patient at the Royal Free Hospital on fresh thyroid glands. As an equally good result followed this mode of treatment it was continued, and in less than three months the disease was scarcely recognizable. Dr. Mackenzie claims for this method that it has advantages over the subcutaneous mode in that it is more readily obtainable, can be more easily carried out, and is free from many of the risks and other disadvantages attendant on the injection of the fluid extract. The thyroids in this case were pounded and given in a little brandy. He showed that it was sufficient to let the patient eat the thyroid or swallow an extract made with glycerine.

* I have been informed that some time back Messrs. Brady and Martin alone were supplying the extract for the use of 100 cases, so there are probably now considerably beyond that number of cases undergoing the treatment.

† The earlier cases have also been tabulated by Dr. Robert A. Lundie on much the same lines as that now presented, and appear with his paper, "The Treatment of Myxœdema," which he read before the Edin. Med. Chir. Soc., and are printed in "The Edin. Med. Journ.," May, 1893.

‡ "Brit. Med. Journ.," August 27th, 1892.

§ "A Case of Myxœdema Treated with Great Benefit by Feeding with Fresh Thyroid Glands." "Brit. Med. Journ.," October 29th, 1892.

At the same time as Dr. Mackenzie reports his case, Dr. E. L. Fox, of Plymouth, reports another case of myxœdema,* whom he had treated at first by the ingestion of a glycerine thyroid extract, and afterwards by lightly fried and minced glands taken in currant jelly. This was followed by a similar result. The treatment was begun on June 2nd, 1892.

Professor Howitz, of Copenhagen,† however, had already carried out this principle, for on March 22nd, 1892, he commenced feeding a patient with the thyroid gland of calves, and he made known his results on July 6th. He, too, adopted this method on the principle that it was more accessible in daily practice, and was a safer form of administering the remedy.

At a meeting of the Clinical Society of London on January 27, 1893, Dr. Arthur Davies showed a case ‡ in the treatment of whom he had employed a further difference in detail. This was the administration by the mouth of a powdered extract obtained by extracting the active principle with glycerine and reducing the resulting extract to a powder by heat. It was Dr. Mackenzie who first suggested its preparation, which was carried out by Mr. Edmund White, pharmaceutist to St. Thomas's Hospital.

These various methods, which differ only in detail, have all been since tried on a number of cases, and they differ little in their result. There is invariably the same remarkable improvement and cure recorded. The extract has been given in a variety of vehicles, such as brandy, beef-tea, water, milk, jelly, with pepper and salt, etc., and the gland has been first subjected to a variable amount of cooking, with the object of rendering it more palatable.

It remains for me to mention one more modification that has been introduced by Vermehren, of Copenhagen.§ He records a case of sporadic cretinism whom he treated with success by the administration of "thyroidin." This substance is obtained by the precipitation with alcohol from a glycerine extract of the finely minced gland, and takes the form of a greyish powder. This substance is, of course, equally applicable to cases of myxœdema, and probably differs little, if at all, from the powder used by Davies.

* "A Case of Myxœdema Treated by taking Extract of Thyroid by the Mouth." "Brit. Med. Journ.," October 29th, 1892.

† "Brit. Med. Journ.," February 4th, 1893, p. 266, and "Semaine Méd.," 8th Fév., 1893.

‡ "Brit. Med. Journ." and "Lancet," Feb. 4, 1893.

§ "Brit. Med. Journ." (Epitome), April 15, 1893. ("Deut. Med. Woch.," March 16, 1893).

With all these various minor modifications there still remains the one disappointing fact that as soon as the treatment is discontinued the patient relapses, so that in a few weeks the patient gradually passes back into the condition of myxœdema from which he has only too lately been resuscitated. So long as the drug is in use, whether it be by hypodermic injection or the ingestion of the gland or a preparation therefrom, so long the improvement continues; but let it be dropped for a time, then without fail do we see only too soon the reappearance of the disease. But it has now been proved that only a small dose is needed to maintain the condition, and that not at very frequent intervals, and the taking of an occasional dose is surely a hardship not hard to bear even were it necessary for the remainder of the patient's life. Although at present there are wanting real indications of a permanent cure, it would seem that after a considerable period the dose may be reduced to a mere trifle, and who knows but that it may finally be dispensed with altogether !*

A Criticism of Published Cases.

(*See Tables* 1*a and* 1*b.*)

For the benefit of those who have not followed the recent discussions I have compiled tables of the cases of myxœdema treated by thyroid injection and feeding that have thus far been published in this country. These, I trust, will be found useful and easy of reference. The main points of each case are arranged under a few convenient headings, viz., the sex and age of the patient, the duration of the disease, the length of time the treatment had been carried out at the time of reporting, the dosage and method of administration employed, the results obtained, and, where such existed, any ill effects that were seen to follow or occur during the course of the treatment. In all there are details of 100 cases shown. A glance at this summary will bring out certain points of interest and importance.

1. The female sex largely predominates, there being only eight male cases, but then it is to be remembered that the disease is far more common in women than in men; the Clinical Society's Report gives the proportion as one to six, but this is undoubtedly too high. The table shows, however, that we may look for equally favourable results in both sexes.

* Such, too, are the views of Dr. Robert Lundie, as contained in an interesting and popular article, "A New Departure in Medical Treatment," which he has lately contributed to "Chambers's Journal," May 6, 1893.

2. There is no limitation of age; the thyroid gland appears to exert the same remarkable influence alike on the young, middle-aged, and those past the prime of life. With regard to the very young I shall have occasion to speak shortly when dealing with the subject of cretinism, and I shall return to the subject of the administration in elderly persons.

3. The length of time during which the disease had existed is seen to make little or no difference. For instance, in Dr. Corkhill's case* the patient is said to have only exhibited signs of the disease five months, whereas in one of the cases reported by Dr. Dunlop† it was of twenty years' duration; between these extremes all stages exist. This is contrary to what might have been expected, and, certainly, at first sight, one would scarcely have hoped to obtain the same marked results where the disease has been a long time in existence. It is, however, in the extremely marked cases that the change is most pronounced, and, on the other hand, the cases in the very earliest stage of the disease seem less noticeably influenced even after a prolonged course of treatment. This point was brought out in the cases published by Dr. G. E. Hale,‡ who wrote me last October: "In three, considerable improvement occurred after periods of seven or eight weeks, all three being able after the course to do a good day's work. In the fourth case, an early case in a young woman, little or no improvement has occurred, although the treatment has been perseveringly followed out for more than six months."

The same applies to two early cases on whom the treatment has been tried in Colney Hatch. They improved slightly after a time, but there was not the rapid change so uniformly noted in advanced cases as being at once observable.

4. The period during which the treatment has been carried out at the time of publication has varied considerably in different cases, from a few weeks to many months, but in all there is the same result recorded. Dr. Murray's is the longest, it is now over two full years, he having begun treatment in April, 1891.§ A most singular point is the rapidity with which a change in the patient's condition is first recognizable, and even a cure may be said to have taken place. The treatment owes its origin to the change that was recorded as occurring within a few hours of the

* "Brit. Med. Journ.," Jan. 7, 1893.
† "Edin. Med. Journ.," May, 1893, p. 1012.
‡ "Brit. Med. Journ.," Dec. 31, 1892.
§ "Lancet," May 13, 1893, p. 1131.

transplantation of the thyroid. The patient under my care seemed brighter within twenty-four hours of the first injection. In Dr. Napier's patient* a change for the better was first noticed after the fourth injection, and the patient was discharged in two months, after sixteen injections of one gramme of a watery extract of the thyroid, with disappearance of all the characteristic signs of the disease. Again, in M. Bouchard's two patients the improvement is said to have been "extraordinarily rapid."† Dr. Mackenzie's first patient "had very considerably altered for the better"‡ at the end of a fortnight's feeding with thyroid glands, and Mr. Shapland's case expressed herself as "feeling better than she had done for years" after taking half an underdone gland every morning for a week.§ Two days after the first injection of ♏xxx. of fluid extract a patient whose photograph and case is published by Dr. Henry, of Lewisham,‖ showed distinct signs of improvement. The changes brought about in one month to eight weeks are always well marked. Again, with two of the more recently exhibited cases, viz., Drs. Wood's and Johnson's, "distinct improvement was discernible on the third day."¶ The length of time during which it may be necessary to continue the treatment is a point as yet unknown. The probabilities, however, are that it may be necessary to continually give a small dose at more or less prolonged intervals in order to maintain the improved state which has been brought about.

5. As to dosage there has been no uniformity, and almost every observer has given according as he thought best. This want of uniformity is, of course, due to the fact that we are still (so to speak) in the experimental stage of the drug, and it has not been found possible as yet to fix the correct dose—that is to say, an amount of the extract which is capable of producing a curative effect without at the same time giving rise to toxic symptoms. The quantity and frequency of administration, however, are points that will probably be shortly decided. At the same time, they will probably depend on the stage of the disease and the age of the individual; moreover, they may possibly vary

* "Notes of a Case of Myxœdema Treated by means of Subcutaneous Injection of an Extract of Sheep's Thyroid," with photographs. "Glasgow Medical Journal," Sept., 1892.

† "Lancet," Oct. 1, 1892.

‡ "Lancet," Jan. 21, 1893.

§ "Brit. Med. Journ.," April 8, 1893.

‖ *Idem.*

¶ "Brit. Med. Journ.," May 6, 1893, pp. 954 and 955.

with individual cases and the idiosyncrasies of the patient. With these varying factors special care will be needed in its employment.

Another point that cannot be decided as yet is the best mode of administering the thyroid gland, or, rather, its active principles. As is shown in the list of published cases, various minor modifications of the original method have been adopted. These, which already have been referred to, have each been lauded as the best by those who first introduced them, and it is only from the experience of others and their more extensive trial that we can arrive at a correct estimation of their proper value. There is no doubt that some of these methods have advantages over others, and that with some there are distinct objections to their use as being more liable to be followed by ill-effects. At the same time, it may be that what is preferable in one case may not be so in another. To this subject I shall return.

6. But what is clear from all the cases that are here collected together is that this special mode of treatment is invariably followed by an improvement in the patient's bodily condition, by a rapid change in the appearance of the patient, and within a remarkably short space of time (measured by a few weeks) the patient has so far recovered from the disease that it is impossible in many cases to recognize the case as one of myxœdema. The general puffy, œdematous-like swelling disappears, and the coarse, dry skin is replaced by one that is smooth, soft and moist, and the blunted, thickened features so characteristic of myxœdema are rapidly lost; the hands become smaller; within a comparatively short space of time young hair commences to grow on the scalp and eyebrows, so that in place of the thin, scanty crisp hair the head is soon covered by a thick healthy crop of hair, which causes a most noticeable alteration in the appearance of the patient. The body-weight rapidly diminishes, often as much as a stone a month, until it has reached a certain point, when it again tends to slightly rise. This loss of weight is probably due to the absorption or conversion of the mucin in the tissues, and the increase which afterwards occurs may be due to a deposit of healthy fat in its place. The special senses all become more acute, eyesight and hearing improve, and general tactile sensation becomes more natural; the bodily functions assume their normal action, the bowels and catamenia become regular, and there is often an increase of urine passed; the voice loses its peculiar slow, thick,

monotonous form, and assumes its original type. The patient becomes warmer and feels more comfortable, and there is a rise of the body temperature, which nearly or quite reaches the normal point. Both mind and body become more active. The patient becomes brighter and more cheerful, and is able to get about and attend to his duties, in which he now takes an interest. This, in short, is only another way of saying that there is a complete transformation, and that the patient has ceased to be a patient, and appears a new individual. Such, briefly, are the results that have been attained.

7. But this startling result has not always been obtained without the occurrence of some grave and unpleasant symptoms. These have doubtless been due in the majority of the cases to an excessive dose of the preparation, manifesting a toxic action, and are capable of, and to a great extent have been overcome by more careful regulation of the dose.

As a rule, when occurring they have been of a mild nature, such as general weakness, faintness, nausea, vomiting, slight giddiness, headache, and aching pains in the neck and shoulders, which have rapidly passed off on reducing the dose, but occasionally the symptoms have assumed a more serious nature, and, at least in four instances, death resulted. This happened in the early days, of the thyroid treatment, and such a result it is to be hoped will not again occur. Amongst the more severe forms of symptoms to be guarded against are loss of consciousness, tonic spasms, collapse, urgent dyspnœa, and cardiac failure. These have been prevented by greater care in regulating the amount and allowing it to be administered more slowly. With a more accurate knowledge of the power and action of the new remedy they are lessened or altogether avoided. The liability to irritation, erysipelas, abscess and induration sometimes following subcutaneous injections has been lessened by greater antiseptic care, and by the more recent administration of the extract by the mouth has been entirely prevented.

As the discomforts and risks of the treatment have been so fully gone into by other writers, notably by Dr. Lundie* and Prof. Grainger Stewart,† I will abstain from further entering on the subject. The latter observer gives some useful advice for the treatment of urgent symptoms that may arise.

But still, I may remark, it is clear that in the active

* "Edin. Med. Journ.," May, 1893.

† "The Practitioner," July, 1893.

principle contained in the thyroid gland we have an exceedingly powerful chemical body, and too much care cannot be exercised in its proper use. In persons suffering from very advanced disease, and in elderly subjects, great caution is necessary, and with returning strength and vigour moderation in all forms of exercise should be insisted upon.*

The Treatment, with Special Reference to the "Insanity of Myxœdema."

The actual number of recorded cases of myxœdema in which definite insanity ensued in the course of the disease is comparatively few,† and only one or two have been published by medical officers of our asylums. But if we remember the mental state which patients who are the unfortunate subjects of myxœdema invariably develop as the disease becomes advanced, we can understand how a considerable number of them eventually find their way into lunatic asylums. It is probable that these institutions are the last home of a large percentage of cases, and there are probably few asylums of any size where such patients do not exist, and, owing to the chronicity of the disease, are probably resident for a long period.

Myxœdematous patients invariably become demented. Dr. Savage, in his review of the Clinical Society's Report on myxœdema in Dr. Tuke's recently published admirable "Dictionary of Psychological Medicine," says:—"In a rather large proportion there is more or less imperfection of

* It would seem impossible that the condition described by Dr. James Whitwell ("Brit. Med. Journ.," Feb. 27, 1892), as found by him in the cortical cells of the brain in a case of myxœdema, can be present except in perhaps the rarest instances, even in the most advanced cases of the disease. Otherwise, how is it possible for the cells to recover to the extent which one would judge must occur with the change in the patients brought about by the thyroid treatment? In like manner it is not easy to explain how the vessels of the brain could recover from such advanced endarteritis and periarteritis as was found to be present in a case of myxœdema by Dr. Rubert Boyce and myself ("Journ. Path. Bact.," No. 2, Oct., 1892). It is clear there is much yet to learn of the pathology and cause of the disease. That such a diseased state of the vessels sometimes exists proves that great care should be exercised in the use of the thyroid juice.

† The following may be referred to:—Clouston, "Clinical Lectures on Mental Diseases," 1883, p. 603. Blandford, "Insanity and its Treatment," 1884, p. 86. Savage, "Journ. Ment. Sc.," Jan., 1880, p. 417. J. C. Mackenzie, "Journ. Ment. Sc.," July, 1889. Ernest White, "Lancet," i., 84, 974. Urquhart, "Lancet," i., 84, 1079. Jürgens, "Lancet," i., 90, 484. Cecil F. Beadles, "Journ. Path. and Bact.," No. 2, 1892. John Macpherson, "Edin. Med. Journ.," May, 1892. James Whitwell, "Brit. Med. Journ.," i., 92, 430.

mental processes, the defect being one of retardation or sluggishness." The development of actual insanity with delusions, sometimes with attacks of excitement, is not uncommon. "Delusions and hallucinations occur in nearly half the cases, mainly where the disease is advanced. Insanity as a complication is noted in about the same proportions. It takes the form of acute or chronic mania, dementia, or melancholia, with a marked predominance of suspicion and self-accusation; exalted ideas may occur. Memory is usually impaired from an early period. It is recorded as deficient in forty-six out of seventy-one cases."*

The authors of many of our text-books on insanity make no reference to myxœdema in its relation to brain disease, and the remainder pass it over in a few words. Dr. Clouston, however, refers to three cases that were under his care at the Royal Edinburgh Asylum for the Insane, "who were positively insane," and adds, "all the examples of the disease I have ever seen were more or less affected mentally, if they were not technically insane."†

No work on insanity to which I have referred speaks of any special treatment for these cases; this is undoubtedly due to the only recently thoroughly recognized, and even then considered incurable disease, and is a feature which will probably receive attention in future editions.

I have already spoken of and commented on a case in which thyroid grafting was adopted with a partial amount of success.

There are now several recorded cases of myxœdema with insanity that have been treated by the subcutaneous injection of the thyroid juice or by feeding.‡ Dr. Ernest Carter, of Whittingham Asylum, was one of the first to report upon the treatment.§ His case was that of a female lunatic aged 43, with myxœdema of over four years' duration, and whose insanity had existed five years. After a three months' course of injections the patient's bodily condition was much improved, but, at the time of writing, complete recovery of her mental power had not taken place. In Dr. Claye

* Tuke's "Dictionary," Vol. ii, p. 828; art., "Myxœdema and Insanity."

† "Clinical Lectures on Mental Diseases," Clouston, 1883, p. 603. In a note in the "Edin. Med. Journ." of May, p. 1057, Dr. Clouston makes mention of eight cases which have been admitted into the asylum.

‡ At Newcastle Dr. Clouston reported two cases of insanity in which improvement was manifest from thyroid feeding; one cured in four months, the other in six.—"Brit. Med. Journ.," Aug. 26th, 1893.

§ "Brit. Med. Journ.," April 16, 1892.

Shaw's case,* however, the patient was discharged from Banstead Asylum, recovered, after a treatment of two months. This also was a female who had showed myxœdematous signs four years, and been the subject of recurrent melancholia for a period of ten years. The case that was under my care at Colney Hatch Asylum, and of which I have elsewhere published the early notes,† had greatly improved in little over a month, if we count from the time the injections were commenced regularly. The change in her mental condition was even more pronounced than that in her bodily, and was one that I never thought it possible to attain.

Dr. Melville Dunlop, of Edinburgh, has published a series of six cases of myxœdema treated by thyroid feeding.‡ One of these (Case II.) was undoubtedly insane at the time. It is a particularly interesting case, and I make no excuse for referring more fully to it.

The case was one of a lady who had shown signs of myxœdema over 12 years, and in whose family there were others affected in the same way, viz., her mother and a twin sister. She had been a complete invalid, and unable to move either her hands or legs for something like eight years. Memory had become defective and she wandered in her talk. A few months before treatment was commenced she became much worse, especially mentally, becoming childish, with hallucinations of sight, smell, and hearing, sleepless, restless, and refused food. At length acute mania supervened, when she was excited and dangerous, and for six weeks had to be under the care of special mental nurses. On October 18th, while in this state, the thyroid feeding was begun. ℿxx. of thyroid extract were administered thrice weekly. "By the 30th of October the excitement had quite gone, and the patient was resting and sleeping quietly. She had no longer any hallucinations, and was speaking rationally." By November 12th there was some improvement in her bodily condition, and the extract was reduced to twice a week. A month later there was a marked change. In January the extract was given only every alternate week. She continued to improve mentally and bodily, and in the early part of February (a four months' course) many of her friends could scarcely recognize her.

Dr. Hamilton C. Marr, of Woodilee Asylum, also reports a case treated by feeding.§

* "Brit. Med. Journ.," Aug. 27, 1892 (communicated by Dr. Stansfield to the annual meeting of the B.M.A. at Nottingham).

† "Brit. Med. Journ.," Dec. 24, 1892.

‡ "Edin. Med. Journ.," May, 1893.

§ "Glasgow Med. Journ.," Aug., 1893.

This is a woman aged 51, whose mental aberration dated from Christmas, 1887, but whose bodily weakness commenced three years previously. She was incoherent and subject to attacks of excitement and violence, at which times she would make false accusations against her attendants. During the intervals she was melancholic and refused to speak. Her health had become very feeble and she had taken to bed. Treatment was commenced in February, 1893, by giving a quarter of a sheep's thyroid mixed with bread crumbs and sherry. After three weeks this was replaced by a glycerine extract, two ounces of which represented one whole gland; of this one drachm was given thrice daily. "The patient gradually improved under treatment," and now it is said that she can converse quite intelligently and is very cheerful in disposition, giving a helping hand to the nurse. Hearing has improved and the swelling of the body has gone down.

Quite recently I have heard of another case of myxœdema with insanity that has undergone the treatment. It is the case which Dr. J. F. Woods, of Hoxton House Asylum,* showed at the Hunterian Society on April 12th.

A female, 32 years of age, with myxœdema of 15 months' duration, of whom it was said that she "began to improve on the third day." Concerning this patient, Dr. S. Whitaker kindly informed me, on August 3rd, that, before treatment was commenced, she had physically most of the signs of myxœdema and "mentally her speech and mental processes were slow, she often heard voices and saw spirits, she was very obstinate, and used to stand or sit about all day and never employed herself. Her weight was 9st. 6½lbs. at the commencement of treatment on January 20th. The treatment was discontinued on June 8th, when her weight was 8st. 6lbs., she had lost most of the physical signs of myxœdema, and mentally she was bright and talkative and employed herself, but she still occasionally heard voices and saw spirits, though not so much as formerly. Since June 8th there has been no apparent change, and to-day (August 3rd) her weight is 8st. 8lbs."

As regards the special mode of administration employed, Dr. Whitaker says that at first the medicine was given twice a week as hypodermic injections of the thyroid extract, but afterwards, and "with better effect," she took White's powders by the mouth. After the first three months the powder was only given occasionally, and during the latter part of the time, in place of the powder, a "thyroid mixture" in ℥ss. doses,† each ℥ss. being equal to ¼th of a gland, and that this seemed to agree with her the best.

* "Brit. Med. Journ.,' May 6, 1893.

† The extract for hypodermic injection was obtained from Brady and Martin, and the "thyroid mixture" prepared by Mr. Chas. Allen.

It is now proposed to let the patient have a dose about once a month.

Under this heading I may perhaps as well call more pointed attention to the change following upon the treatment that has taken place in the mental condition of those patients who have not been regarded as insane, but who have shown the more or less marked dementia that is characteristic of advanced myxœdema. Thought, like speech and actions, is slow, and memory is impaired or lost, and sometimes there are distinct delusions of a suspicious nature, which yet are not sufficient to have the patient certified as a lunatic.

In all these cases, as I have already said, the patient becomes brighter and the mind more active; memory returns and delusions have frequently been lost. Some of these cases will be found referred to elsewhere in the present paper. Drs. Murray, Mackenzie, Davies, Maude, and others all bear testimony to the unquestionable mental improvement that invariably occurs, and as Dr. Hingston Fox says of his patient, "not only has the physical condition altered, but mentally the change is also great. She feels much lighter, less burdened, as she says, and the depression of spirits has largely passed away."* In a note I received on May 18th Dr. Davies tells me that in one of his cases the mental activity for carrying out arithmetical calculations was greatly increased by the treatment, and in others the hearing has been very markedly improved.

Seeing what has thus been done in this line, it appears to me only right that an attempt should be made in these cases to allow the patient the benefit of a trial of one or other of the methods employed in the treatment, and in our asylums should certainly be carried out as a treatment for the insanity of myxœdema.

Although I do not intend to enter on the pathology of myxœdema in the present paper, one cannot help remarking that we can see, in the results that have recently been obtained, strong evidence in favour of the view that the insanity of these cases is dependent primarily, if not entirely, on the disease or atrophy of the thyroid gland and not on a primary change in the brain.†

* "Trans. Hunterian Soc.," 1892-3.

† I would suggest that in those few cases where insanity antecedes the appearances of myxœdema, the presence of the two diseases is a mere coincidence.

The Thyroid Gland in the Treatment of Cretinism.

(*See Table II.*)

Just a word or two on the subject of congenital myxœdema, or sporadic cretinism, as it is more commonly called in this country. Fortunately such cases are of less frequency than myxœdema in the adult. Of the number in this country I have no idea, but there are probably some in all our imbecile asylums. I have seen two quite recently at Leavesden. They were both males, and showed the disease in its characteristic form. Children born in that condition have been thought hopelessly imbecile, and quite incurable. They have lived a wretched, automatic existence for a variable length of time, rarely reaching beyond 30 years of age, as a rule being ultimately carried off in the winter months. No treatment beyond attempting to keep them warm by clothing and surroundings has hitherto been considered of use.

Victor Horsley, who contributes an interesting article on cretinism in the "Dictionary of Psychological Medicine," says: "A good deal can be done in the direction of palliation" by keeping the patient very warm in a hot atmosphere, thoroughly clothed, the employment of hot air and Turkish baths, and the internal administration of pilocarpine or tincture of jaborandi.

Now we can look for a better result. Horsley, writing on the same subject, remarks: "No treatment of cretinism has ever been attempted from the point of view suggested by the pathology, for the reason that until recently the latter has been so extremely obscure. It is obvious, however, that where the idiotic condition can be shown to be originated by loss of function of the thyroid body, an attempt should be made to restore that function. The only way in which this would be possible would be by the method originally suggested by Prof. Schiff, viz., transplantation of the thyroid gland."*

Cases have lately been published in which the thyroid treatment has been carried out with a marked change in the condition of the patient.

Dr. John Gibson, of Brisbane, records the following case:—

Male cretin, aged seven years, on whom he had twice grafted the thyroid gland from a lamb, first into the right mammary region on July 20, 1891, and again on May 20, 1892, he introduced

* "Dictionary of Psychological Medicine," Hack Tuke, 1892.

a gland into the peritoneal cavity. The paper which he originally read before the Intercolonial Medical Congress of Australia last year was published in this country last January.* The numerous accompanying illustrations, reproduced from photographs, show a marked change in the appearance of the child, a brighter and more intellectual look is especially noticeable. He had grown two inches. Four months after the second grafting Gibson concludes his remarks by, "To all appearance he is now merely a well nourished baby boy, with soft, natural skin, and firm limbs, with somewhat thick features and lips, but no myxœdematous swelling. The grafting, to sum up shortly, has cured his myxœdema, and has lessened his cretinism."

Only a few months ago the following case was published by Dr. Edward Carmichael, of Edinburgh† :—

Cretin about nine years of age. Patient was treated with the hypodermic injection of thyroid extract. Commencing in April, 1892, the injections were continued until October, when feeding with the raw gland was substituted. The accompanying photographs show a marvellous effect, and the observer states that "The result of the thyroid treatment was continuous improvement. As week by week passed some mark of improvement was always seen. Marked improvement in intelligence was seen in many little actions." The patient could not be recognized by friends as the same child.

These two cases show what may be expected, no matter which mode of introducing the thyroid is preferred. In addition to these, Dr. Affleck‡ showed at Edinburgh "a case of sporadic cretinism in a young man which had been greatly improved by implantation of thyroid on three occasions." Dr. John Thomson§ has treated a couple of cretins, aged respectively four and 18 years, by feeding, with "wonderful success." Dr. Byrom Bramwell showed a girl aged $8\frac{1}{2}$ years at the Edin. Med. Chir. Soc., on February 16, whose "mental condition had become completely transformed," and who had grown an inch in height after five weeks of thyroid feeding.‖ It was on a case of adult female

* "The Function of the Thyroid Gland, with Observations on a Case of Thyroid Grafting," "Brit. Med. Journ.," Jan. 14, 1893.

† "Cretinism Treated by the Hypodermic Injection of Thyroid Extract and by Feeding," "Lancet," March 18th, 1893.

‡ "Brit. Med. Journ.," Feb. 25, 1893, p. 411, and "Edin. Med. Journ.," May.

§ "Brit. Med. Journ." and "Lancet," Feb. 25, 1893, and "Edin. Med. Journ.," May. The latter case is reported in full on p. 1022, and is accompanied by illustrations.

‖ "Edin. Med. Journ.," May, 1893, p. 992.

cretin that Vermehren, of Copenhagen,* used, with success, the preparation which he has called "Thyroidin," and he has since used it with like result on another. Dr. A. G. Francis, of Hull, has informed me of a case of congenital myxœdema, as much as 36 years of age, whom he has under his care, and who "is improving immensely" under thyroid treatment.†

There is one more case recorded in which the thyroid has been employed in the treatment of cretinism. This was the case of Dr. V. Robin, of Lyons.‡ The fresh juice from sheep's thyroids was injected daily into a child of seven years of age. "Improvement was immediate. In fact the child is quite unrecognizable to those who knew it before treatment." The injections were afterwards supplemented by successfully grafting two lobes of a sheep's thyroid in the submammary region.

Dr. William Robinson, of Darlington, has not been so successful. He informs me that the case of sporadic cretin that he referred to in the "Brit. Med. Journ."§ as being slightly improved by thyroid extract was a female aged $10\frac{1}{2}$ years, who had weekly injections of an extract prepared in accordance with Dr. G. Murray's directions. The dose was given beginning with six and increasing up to thirty minims for two months, after which one thyroid gland was eaten weekly for several weeks. The result was only very slight improvement—"not sufficient to justify further treatment." In a second case, a male semi-cretin, aged 28 years, there was "no visible improvement" after a similar two months' course of hypodermic injections.

Although the result here was disappointing, and also in a male cretin, aged eight, who was referred to by Mr. Evans at a meeting of a medical society on March 24th, "who for six weeks had taken one thyroid lobe twice a week without any improvement,"‖ such a result appears to be rather the exception than the rule, and we may expect to see great benefit derived from the new treatment in this supposed incurable disease. It is possible that by applying the remedy after the manner of Robin the best results are to be obtained.

* "Brit. Med. Journ." (Epitome), April 15, 1893, and "Deut. Med. Woch.," March 16, 1893.

† "Brit. Med. Journ.," April 8, 1893, and Private Letter dated Aug. 5th.

‡ "Brit. Med. Journ." (Epitome), Sept. 10, 1892, and "Lyon. Méd.," Aug. 7, 1892.

§ "Brit. Med. Journ.," Jan. 7, 1893, p. 38.

‖ "Brit. Med. Journ.," April 8, 1893, p. 767.

Personal Experience of the Treatment in Myxœdema with Insanity.

It has been my good fortune to see four cases of myxœdema treated by this modern method in Colney Hatch Asylum during the past twelve months, and so I have been able to notice closely what changes and improvement actually took place in the patient's condition, both bodily and mentally.

Of the four cases in Colney Hatch, one is that of a woman in an advanced stage of myxœdema, whom I myself treated, and whose case I reported in the "British Medical Journal" for December 24, 1892, two were women in an early stage of the disease, and the remaining case is that of a man presenting all the well-marked characters of fully-developed myxœdema.

I. First let me refer again to my case of M. B. She was a woman of 50 years of age, with myxœdema of at least eight years' existence, and whose insanity, which took the form of religious melancholia, was of $4\frac{1}{2}$ years' duration. After treatment by subcutaneous injections of thyroid extract, extending over three months, there was great change in her bodily appearance, but the improvement in her mental condition was even more marked. She was cheerful, bright, usefully employed, free from all delusions, and might be considered quite sane; if there had been friends anxious to take her out of the asylum there is no reason why they should not have done so.

After October 4th the injections were discontinued, and unfortunately nothing was done to maintain the improved condition brought about. In a short time the patient slowly but steadily relapsed—that is to say, there was some return to the myxœdematous appearance that she previously possessed; her voice became somewhat thicker, hearing less acute, puffiness of face more marked, slower in movements, and she did not feel in such good health, and with this a drop of the temperature again, nearly to its original low position. But she never reached anything like the stage present before the injections were commenced. It is satisfactory to note that her mind was still clear, and has remained so all along.

On February 28th the treatment was renewed in another form. On that day Dr. Seward gave the patient a thyroid powder, representing $\frac{1}{6}$ of an entire thyroid gland of a sheep.* Between then and May 9th the patient took 17 similar powders. She then had her photograph taken, which is reproduced as Fig. 2, and for contrast to show the striking change that has taken place in the

* Supplied under the direction of Mr. Edmund White by C. B. Allen, Pharmaceutical Chemist, Kilburn.

Fig. 1. M.B. Before commencing treatment.

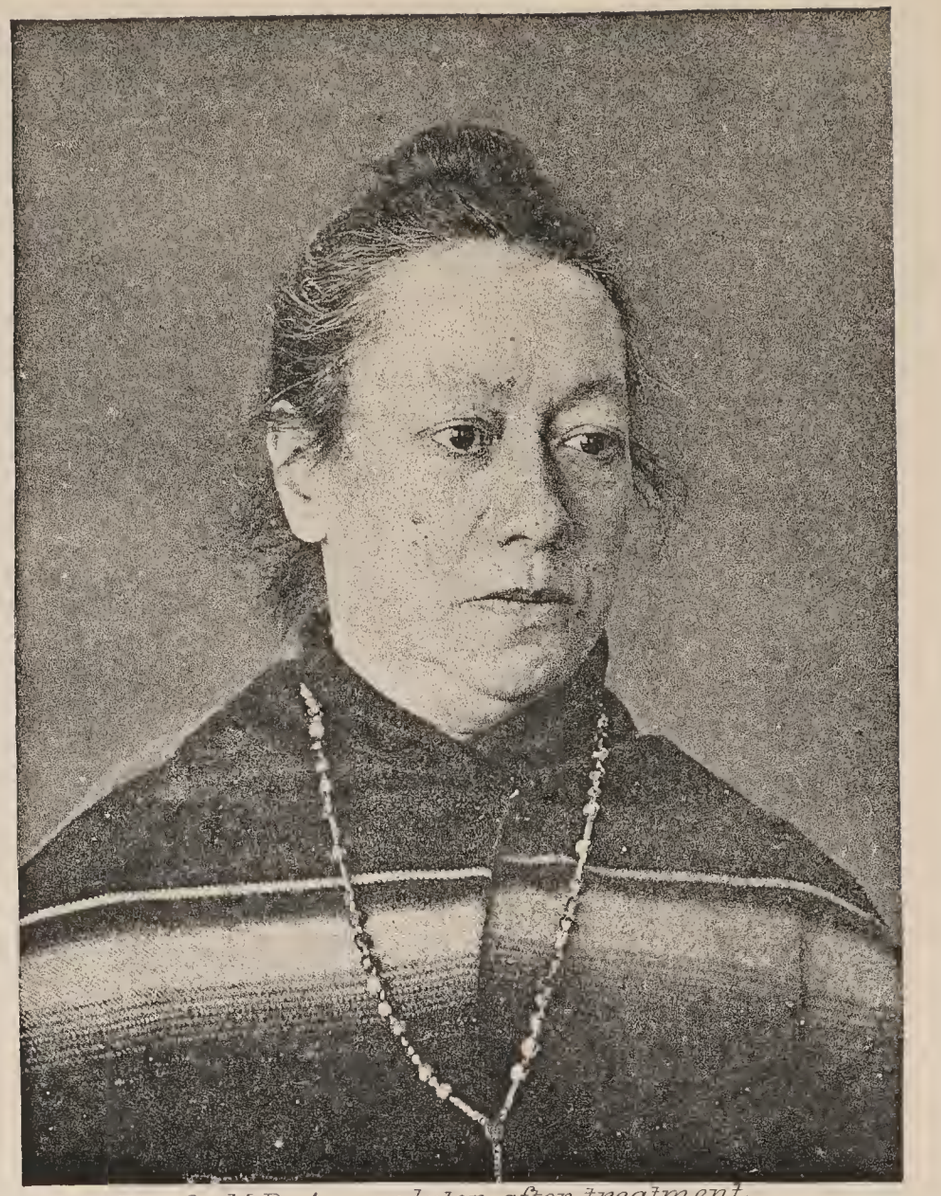


Fig. 2. M.B. A year later: after treatment.

CASE OF MYXŒDEMA.

Engraved by Danielsson & Cº London.

patient's condition Fig. 1 is reproduced from a photograph that was taken of the patient before any treatment was commenced, exactly 12 months previously. It may be mentioned that at that time the patient was quite unable to open her eyes owing to the swollen state of her eyelids, and her mind was such that she did not know what was being done, and she has since had no recollection of the event. Her earlier days in the asylum are a perfect blank, from which she was first awakened by the thyroid injections, only, however, to recall events that took place before her admission. In the last photograph taken she has much the same appearance as she had when the hypodermic injections were first discontinued, an appearance which she still maintains.

The patient has now (Aug. 5) had the powders on 33 occasions; first at intervals of two or three days, then every fourth day, and now for the last six weeks not oftener than every fifth day. This is found to keep the temperature as nearly as possible at normal; in fact, during the past week there has been a tendency to rise above it. The last three months she has had three grains of a powder obtained from another firm of druggists,* which has answered equally well. She has always taken the powder in jam after breakfast, and on those days remains in bed until mid-day.

The patient's improved condition is maintained, and she now shows only a very slight degree of the myxœdematous facies, but she is somewhat crippled owing to the old rheumatoid arthritis from which she suffered before the myxœdematous process started; she is, however, able to get about and make herself useful in the ward. She is quite sensible in her speech, and is very cheerful, and she regards her present condition as a happy release from her former wretched state.

Mentally she would be described only as somewhat weak-minded.

The action of the drug upon her joints is remarkable. She suffers intense pain in all her joints after the powders are taken, although recently, perhaps, to rather a less degree. This comes on shortly after the powder is swallowed, and continues for the greater part of the day. This has not been noted in any previously recorded case, and is probably due to the chronic rheumatoid affection of her joints, which remain permanently enlarged and deformed.

The patient's weight, which, after a month's regular injections, fell from 9st. 12lbs. to 8st. 8lbs. (August, 1892), has since gradually increased, and on May 18th had reached 10st. 8lb., notwithstanding the absence of much of the œdema. This has been maintained.

From charts, with a complete record of the patient's tempera-

* Prepared by Ferris and Co., of Bristol, who with a number of other firms now supply several preparations of the thyroid.

ture since she first went under the thyroid treatment (May 10th, 1892), it is seen that the original subnormal temperature gradually rose and remained about normal so long as the injections were continued, and for a few weeks beyond, after which it again fell to its previous low position, to again ascend when the powders were administered. On a separate chart there was recorded the rise of temperature that followed in the course of the day after the powder was given, the temperature being taken every two hours. It is interesting to note that (as in the case with injections), after the early administrations, there is a very sudden rise and fall again of the temperature, which after a time becomes much less as the normal is maintained, and recently it has only risen a few points during the day.

The two early cases of myxœdema were treated in different ways.

II.—The first is that of L. B., a female, aged 51, who was admitted into Colney Hatch, April 8th, 1892, for melancholia. She was irritable, restless, and quarrelsome, with delusions of suspicion. She had attempted to commit suicide. She was a Jewess and had been married. She presented the signs of the disease in an early stage; there was slight puffiness of her face, the skin somewhat thickened, dry and rough, and her hands large and swollen. Hair scanty and rough. Her voice was inclined to be thick, slow and monotonous, and she was somewhat deaf. Her temperature was sub-normal, never reaching the normal line. Weight, 9st. 11lbs.

While this patient was under my care I treated her by the hypodermic injection of the fluid extract, obtained, as in the case of the other, from Brady and Martin, of Newcastle. Between the 29th August and 4th October she was given 14 injections of ℥xx. each, there being an interval of a day between each, with a few exceptions. She objected strongly to the injections, not because they hurt, but because, she said, that she was "marked for life, and would be turned out into the streets as a thief." At the end of this time there was an undoubted slight degree of change noticeable, although she could not be said to have recovered her senses. Her body temperature rose to a more normal position, and her mental faculties were much clearer. It is possible that further improvement might have followed if the treatment had only been persisted in, but unfortunately it was allowed to drop, and what little improvement had been produced has more or less disappeared, and she is now in nearly the same condition as she was in last August.

III.—The other female patient, M. S., was treated by my colleague, Mr. H. G. Shaw, by the ingestion of raw thyroids. She had been resident in the asylum since December, 1890. She was a

single woman, 45 years of age. She was restless, complained of noises in her head, and had aural hallucinations and optical delusions, and others of suspicion. It had been noticed that her features had been gradually assuming a rather more thickened aspect, and her voice was thicker and more monotonous in character than on admission. She was becoming more languid and slower in her movements, and she suffered much from cold, always being worse when the day was chilly. Her temperature was found to be seldom much above 97°.

It was decided, therefore, to try the effect of the raw gland on her. Commencing in October last, she continued to have them at intervals of one and then two days, for a period of six weeks, on eight different occasions. She took them minced in the form of sandwiches. After the first once or twice she complained of headache and giddiness, but after the later three administrations the ill-effects assumed a more grave form; she had violent pain in the abdomen, followed by loss of consciousness. The administration was, therefore, stopped. For a fortnight the patient remained in bed in a somewhat critical condition, and as during this short course of treatment she lost considerably over two stone in weight, there cannot be the slightest doubt but that the drug was too rapidly pushed, and that better effects might have been expected from a smaller dose. But it is by such experiences that we learn. On November 21st, 1892, it is noted that "a considerable improvement, both mentally and physically, has followed." This patient is now in very good health, but still shows some signs of the myxœdema, although to less degree than last October. She says herself that she is certainly feeling better than she did at that time; she has also been gaining in weight, and in May a luxuriant crop of new hair sprung up on her head. Her mind is clear, she is useful in the ward, and is always willing to oblige.

IV.—I now come to the case of the man suffering from advanced myxœdema, who is now under the care of Mr. F. Bryan, and who will publish the case in full. The patient, J. T., is 33 years of age, and has been an inmate of the asylum six years, being admitted for melancholia, with aural hallucinations and suicidal attempt. In the original certificate it is stated that this condition seems to have arisen from concussion of the brain, the result of accident. From the note made on admission it is evident that myxœdema was present, but not recognized, and it is said that his condition was "suggestive of chronic kidney disease." From further notes it is clear that the myxœdema became more marked, and still remained unsuspected until September 1892, when it was proposed to let him undergo a course of treatment by the thyroid method (injections), but some difficulty arose in having the patient photographed before commencing the treatment, and it was consequently postponed for a time. Meantime the administration of a powder had been proposed, and proved to be followed by as marked

results as that following the injection method, and so it was decided to carry out this mode of administration on the patient.

Treatment was commenced on February 25th of this year, and is being continued at the present time. During the three months that had elapsed, up to May 6th, the patient had taken 23 powders (White's) similar to those used in the case of M. B.; for the first three weeks he had a powder every other day, afterwards one every fourth day. From May 8th to May 23rd half a powder every other day was taken. On May 25th it was altered to five grains (Ferris) every other day, which was continued until June 18th, when the temperature rose to 101°, and there was severe vomiting. For three days the patient felt very ill, and his temperature remained high; it then fell to 96·4°. Similar powders were commenced again on June 26th, and he had one a week, which has lately been increased to two. Up to the present time (August 5th) he has had the drug on 52 occasions, when he has remained in bed during the morning.

At the time of commencing the treatment the patient had the appearance of a typical case of fully-developed myxœdema, so that there is no need to repeat a minute description of his appearance. By May he had altered to a wonderful extent; he was more healthy-looking, and had lost the characteristic look almost entirely. His hair had grown so that it was quite thick; his voice was clearer, his eyesight improved, and he did not have sudden attacks of blindness, of which he formerly complained. The patient said himself that he was feeling much stronger and better in health, warmer and more comfortable. He had now lost the weakness of which he complained at first after taking the powders.

This condition is being fully maintained. The man is sensible, and appears to be almost if not quite free from delusions. He says that six years ago he was taken to the Middlesex Hospital owing to an accident that befell him, and he remembers being spoken of at that time as a case of myxœdema.

The patient's weight gradually fell from 10st. 12lbs. on February 25th to 9st. 7lbs. on April 29th. Since that date it has been rising, and has now reached 10st. 3lbs. Before treatment his temperature was almost invariably below the 97 line; after the commencement of the treatment it rose to the 98 line, and for some time remained between 98° and 98·4°, but now it varies between 97° and 98°. It is also interesting to note a distinct increase in the urine passed during the 24 hours; the amount has gradually risen from about 50ozs. in February to 70ozs. in August.

Beyond the first weakness and the attack of vomiting, with rise of temperature that once occurred, the patient has been quite free from ill-effects.

Other Cases of Myxœdema treated with Thyroid Preparations.

Besides the cases just described, which we have and still are treating in Colney Hatch, I can speak from personal experience of the great change and benefit which I have seen in several others thus treated.

I am able to add a few short notes of one or two cases that have not yet been published.* The first of these is particularly interesting on account of the patient's family history, where close relatives were affected either with insanity, imbecility, or Graves' disease. For these notes I am indebted to Dr. A. Maude, of Westerham, who is the author of several papers on Graves' disease. In the second case the patient herself had been the subject of this disease only a short time previously. Dr. Wilkin Stabb, of Torquay, kindly sent me the notes. In connection with the subject of Graves' disease, it may be mentioned that Dr. Duke's † patient had a goitre on the right side, and Dr. Putnam's second case ‡ had an enlarged thyroid, and suffered from tachycardia, but had no exophthalmos. In the latter case we are told that the thyroid decreased in size with the rapid improvement that took place, and also that there was a strong history of myxœdema in the family.

I.—Mrs. J., a labourer's wife, aged 60, has been under the observation of Dr. Maude § since June, 1887. The onset of myxœdema was very gradual, apparently beginning in 1888. In December last the case presented a large number of the symptoms of the disease as given in the Clin. Soc. Report, but the facial change was never very highly marked. She may be described as an early, slow case of myxœdema, whose mental state was that of chronic dementia with suspicions of neglect and conspiracy rather than the usual mental state. She had some chronic arthritis and emphysema, and at intervals attacks of "stupor" had occurred.

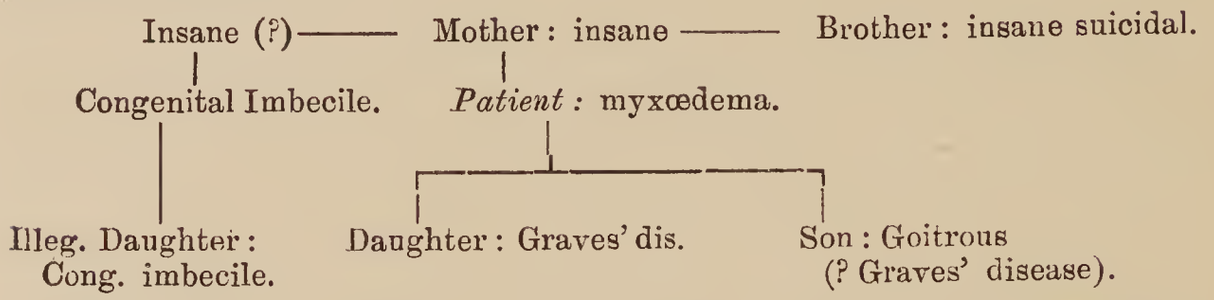
* In the "Table of Published Cases" it is to be noted that where an asterisk is affixed to a number it indicates that additional information has been added to those cases than is obtainable from the references given. For these extra facts, now for the first time published, I am indebted to the physician whose care the patient was under, and who reported or showed the case in the first instance.

† "Birmingham Med. Rev.," Aug., 1893.

‡ "American Journ. Med. Sc.," Aug., 1893. Dr. Putnam also refers briefly to three cases of acromegalia who were improved by taking thyroids, and he quotes from Drs. Barron and Stattuck that they had used the gland with benefit in simple obesity.

§ The patient was shown at the South Eastern Br. B.M. A. on May 11, 1893. See "Brit. Med. Journ.," May 6, 1893.

The family history of this patient was very neurotic, and may be thus represented:—



Treatment was commenced on December 10th, 1892, by thyroid feeding, raw sheep's thyroids being given pounded as follows:—

Dec. 10, ,, 14, Jan. 3, ,, 10, ,, 17, ,, 24 — One thyroid at 11 a.m. The pulse always rose to over 100, and occasionally the patient sweated freely after the dose.

Feb. 1.—Two thyroids. The patient became very faint and collapsed, and her pulse increased to 130, and became very irregular.

Feb. 7.—Has lost flesh considerably. Skin warm and moist. Mental state improved.

April 1.—Relapsing rapidly.

May 4.—Very lethargic.

May 5.—Treatment was begun with Burroughs and Wellcome's tabloids. Two tabloids, representing 5grs. each, every day, and continued for ten days.

With regard to the ill-effects, both the raw glands and the tabloids produced great occipital headache, faintness, and a general sense of discomfort, but the former alone caused sickness. The arthritis, which was always of a slight and passive form, with no marked articular effusion and pain, but great knottiness and thickening of the fingers, was not affected by the treatment (as in my case of M. B.). The pain produced by the thyroid extract was not in the joints, but apparently a general muscular pain. As regards the occipital pain, an exceedingly common symptom, Dr. Maude remarks that it does not seem to be superficial, and suggests that it is probably due to distension of the torcula and sinuses at the back of the skull.

Dr. Maude will not express a decided opinion as to whether his patient was insane apart from the myxœdema or whether insanity pre-existed, as the onset of the mental state and the swelling, etc., were both so gradual. He says that he had an impression quite two years before he made up his mind that she had myxœdema, that she had primary dementia, but he goes on to remark that primary dementia in a woman of that age is unlikely, it being more likely that the dementia was myxœdematous all along.

Although the improvement that has so far occurred in the patient's condition was not as marked as in many that have been reported, yet her mental state is much improved. "She can now (Aug. 10) work in the house, keep up a sustained conversation on simple matters such as the weather, her health, or the conduct of her neighbours, and has no delusions at all, though she remains very grumbling and complaining. A point worth noting is that as she improves under treatment she acquires more of that fatuous bonhommie which myxœdematous people often have."

Pilocarpin had previously proved a complete failure.

II.—A female (spinster) aged 22, who has been under the care of and been treated by Dr. Wilkin Stabb,* had had exophthalmic goitre for eight years. This, however, disappeared after an attack of measles, and was followed by the slow development of a condition which was diagnosed by Dr. Ord in December, 1891, as that of myxœdema. The symptoms of this latter probably commenced in the beginning of 1890. Dr. Stabb commenced treatment on December 20, 1892, and is still continuing it in a modified form. At first he gave half a gland (one lobe) twice a week, coarsely minced and covered with port wine and water, $2\frac{1}{2}$ hours after a meal. On three occasions a whole gland was given at a time, and once she had four glands within seven days. Sometimes treatment was omitted for a few days, and tonics given in place of the thyroids, on account of a feeling of malaise and rapidity of pulse. The patient is now (August 5) taking "White's powders," being equivalent to $\frac{1}{3}$ gland once a week.

The results obtained so far are briefly thus:—The skin acted slightly after the first, and freely after the second dose. As regards weight, the patient lost $13\frac{1}{4}$lbs. in just a month, but has regained it since. Her pulse rose from 70 to 100 and 120, speech became normal, lips thinned, hair less dry, malar flush departed, and she ceased to feel cold. The temperature, which before treatment varied irregularly between 94° and 97°, was the last symptom to show any definite improvement, but it is now always above 97°, and is generally about 98°. She seems now to be a healthy person. The only ill-effect noticed was an increased lassitude during the first month of treatment.

III.—Dr. A. Barron says of his first patient,† after having the juice of half a sheep's thyroid subcutaneously once a week for four months, that she appeared to have returned to her normal condition, and that her weight fell from 12st. 7lb. to 10st. 2lb. The treatment was begun in May, 1892, and now (August 10, 1893) she appeared to be perfectly well, and has a fairly respectable head of hair. There have been no ill-effects. The injections

* Who referred to the case at the South Western Br. B.M. A. on April 13, 1893. See "Brit. Med. Journ.," May 6, 1893.

† "Brit. Med. Journ.," Dec. 24, 1892.

have been given up, and in their place the patient takes six Burroughs and Wellcome's tabloids every Sunday.

IV.—Mr. William Dobbin says that his case, who was referred to in the "Brit. Med. Journ.,"* was a female of about 40 years of age, with myxœdema of from four to five years' duration. For about six months he prepared an extract of the thyroid according to the formula of Dr. G. Murray, and administered it twice a week hypodermically. After trying minced raw thyroid, which, however, could not be borne as it produced diarrhœa, he used the juice prepared after Hector Mackenzie's method, viz., thyroid macerated in tepid water, strained through muslin, and given in beef tea. Lately tabloids of Burroughs and Wellcome, three twice a day, have been substituted. There have been no ill-effects, except once there was an abscess after injection.

The result has been that the swelling has diminished, unsteadiness of gait removed, and very fair health recovered. The patient can now (August 10, 1893), after about thirteen months of treatment, attend to her domestic duties; she enjoys life, and considers herself well.

Dr. Mackenzie has informed me that amongst cases he has seen treated, in one, that of an old lady, where the disease was of old standing, very little improvement took place, but there was really very little amiss with the patient. In another case improvement was only partial, and although the swelling disappeared and the hair grew, the patient remained very feeble. He adds that "in every case the mental improvement has been unquestionable."

Dr. Arthur Davies, who has had considerable experience with the new treatment, has kindly sent me the following brief notes of the seven cases of myxœdema whom he has treated by thyroid extract given hypodermically and by feeding with dried thyroid powder or tabloids. As will be seen from the "Table of Published Cases," most of these have been shown or described elsewhere, but in these notes there is contained some additional information of interest, and at the same time they are brought up to date (Aug. 10, 1893). We thus know the present condition of the patients.

I.—G. W., male, married, age 43; duration of disease 12 years. Treated by hypodermic injections of thyroid extract. Improvement very remarkable after three months, and the patient was scarcely recognizable. Tendency to relapse after six weeks' interval, but again improved under treatment. No bad effects whatever. Under treatment one and a half year.

II.—Alice A., married, age 46; duration seven years. Greatly

* "Brit. Med. Journ.," Feb. 4, 1893.

improved after three months' treatment by hypodermic injections. Tendency to relapse after five weeks' cessation, then put on tabloids and improvement again marked. No bad symptoms. Under treatment one year.

III.—Ada B., single, age 47; duration six years. Treated by thyroid powders. Very great improvement and patient hardly recognizable. No tendency to relapse after five weeks. Rapid loss of weight—four stone in 10 weeks. Under treatment seven months.

IV.—Joseph M., married, age 45; duration five to six years. Treated with thyroid powders. Very marked improvement and patient not recognizable. All trace of myxœdema was gone in three months. No bad symptoms. Under treatment seven months. No tendency to relapse as yet.

V.—May B., married, age 59; duration 10 years. No trace of myxœdema after three months' treatment by thyroid tabloids. No bad effects. Tendency to relapse after six weeks, but again improved under treatment. Total time of treatment seven months.

VI.—Alice T., married, age 54; duration four years. Improved markedly after taking thyroid tabloids. Under treatment four months.

VII.—Susan P., age 43; duration eight years. Improved at first for six weeks under injections. Patient lost sight of for two months, then put on thyroid tabloids and again improved. Under treatment on and off for 16 months.

Comparison of the Various Methods: General Conclusions.

There can be no doubt as to the advantages which the thyroid treatment holds over every other drug or mode of treatment in this disease, and in conclusion it only remains to say a word or two as to the best method of administering this new but powerful remedy.

Already I have passed in review with more or less fulness the various methods that have been proposed. They may be summarized as follows:—

1. Thyroid grafting.
2. Subcutaneous injection of an extract of the thyroid gland.
3. Ingestion of an extract (aqueous or glycerine) of the thyroid gland.
4. Ingestion of thyroid gland, raw or slightly cooked.
5. Ingestion of a dry extract obtained from the thyroid gland, in the form of a powder, tabloid or capsule, or pill.
6. Ingestion of thyroidin.

Of thyroid grafting I think I have said sufficient to show that so far the results obtained have, in a manner, been disappointing and scarcely what at one time was hoped of it. They have certainly not been followed by the same striking results as those ensuing from the more recent methods adopted. At the same time considering the fact that the treatment by these latter is not a permanent cure, and that the drug has to be taken at certain intervals in order to maintain the improved condition brought about (a fact which is easy to understand), it would seem that our only hope of a permanent cure for myxœdema lies in some method by which transplantation can be brought to greater perfection and the graft made capable of living in its new position. Professor Horsley, at Newcastle, has lately called attention to this when he said * that "it would appear more reasonable to perform transplantation after a prefatory treatment by feeding or injection so as to provide that the grafted gland should be embedded in normal connective tissue and not in diseased tissue."

By the injection of a fluid extract subcutaneously the treatment became at once more simple and free from the many risks of a large operation. It was a small operation that no physician would mind undertaking, and its immediate effects were much more striking. Moreover, it has been shown that the cure could be maintained by the occasional use of a smaller amount than that first employed, and the ill effects that followed its use in many of the earlier cases have been shown to be much lessened or avoided by the more careful use of the fluid and by paying greater heed to the regulation of the dose, and to the subject on whom it was being used.

A watery or a glycerine extract appears to be equally efficacious, and either can be made without a great amount of trouble, although it is perhaps better to obtain it at regular intervals from some druggist of repute, several of whom now supply it at a moderate cost.

With regard to the best dose to employ this would depend on circumstances, such as the age of the patient, duration of the disease, and various other small points that can only be decided in individual instances. Dr. Murray, at the Clinical Society, said he now injected about ℥xv. at a time, very slowly, which caused less irritation than a larger dose,

* Report of Annual Meeting of Brit. Med. Assoc. at Newcastle-on-Tyne, "Lancet," Aug. 5, 1893.

and in order to maintain the patient in health he recommended the use of a much smaller dose.* In this latter, which he called the second stage of the treatment, he had also given the extract by the mouth—daily doses of ℥x. given in water—and on another occasion † "he urged a small dose daily rather than a large dose at longer intervals."

Although the ingestion of thyroid glands, whether raw or slightly cooked, appears perhaps the simplest method possible, it certainly is not without drawbacks. The principal of these is the difficulty of giving a fixed dose. In some cases in which this method has been employed bad symptoms have followed. And as the thyroid glands vary greatly in size, not only in different animals, but also in the same species,‡ and probably also vary in their activity with the age of the animal and other circumstances, if the patient be allowed to procure the gland themselves their eating may be followed by results of a very unfavourable nature. It is essential, therefore, that when used they should be ordered by the medical attendant, and whilst being employed the patient should remain constantly under his observation. When the raw glands are given they should not be more than one lobe of the thyroid two or three times a week, as recommended by Drs. Pasteur and Calvert.§

Dr. Hector Mackenzie does not now allow the raw gland to be eaten, as it has given rise to gastro-intestinal symptoms, but gives his patient a freshly-made extract. Writing with regard to his first case, in a private letter on May 5th, he said, "My patient is keeping very well. I don't think anyone seeing her now would suspect her to be a case of myxœdema. In fact, within a few weeks of the commencement of the treatment the characteristic appearance of symptoms had disappeared. She continues to have a freshly prepared liquid extract of the gland once a week. She comes up to the hospital where the nurse prepares the extract for her, simply mincing it up finely, letting it stand for a time in some beef tea and then straining. The catamenia have lately returned after an absence of five years."

* "Lancet," Feb. 4, 1893, p. 248.

† "Brit. Med. Journ.," Feb. 25, 1893, p. 411. See also Dr. Murray's illustrated paper on "The Treatment of Myxœdema and Cretinism," "Lancet," May 13, 1893.

‡ See "Lancet," Feb. 4, 1893, p. 274.

§ "Clinical Society," Jan. 27, 1893; "Lancet," Feb. 4, 1893.

Again, on August 5, he says that his "original patient" was in very good health and there were no signs of myxœdema whatever. Lately she has been having the expressed juice of a whole thyroid gland once a week, and occasionally "White's thyroid powders" were substituted (three a week, the equivalent of half a gland). She, however, preferred the fresh extract.

The use of the extract in the form of a powder is a distinct advantage in several respects. It is a grey tasteless powder which will keep good for a sufficient period. It can be given in a variety of vehicles. It is prepared in a scientific way,* so the dose can be accurately measured. The results from its employment have been as satisfactory as those otherwise obtained. Or, if preferred, tabloids prepared by compressing the powder can now be obtained, each being equivalent to five grains of the fresh thyroid.† They have received considerable favour.

Dr. Arthur Davies wrote me under date May 9th:—"As regards the cases I have treated solely by giving the dried thyroid extract, each one is still in a vastly improved state; indeed, one may now say that there is no sign or symptom of myxœdema in them. I am keeping up the treatment, but by degrees gradually lessening the frequency of the dose. I formerly gave White's powders, but now use Burroughs and Wellcome's tabloids, which I find equally efficacious, though perhaps slower in action. Of course, as regards rapidity of treatment, the subcutaneous injection is the most quick." Whichever way is preferred, the rapidity of the recovery appears to depend upon the amount of the extract employed. It is possible, however, that by giving the extract in smaller quantities over a longer period that a less rapid recovery will be found to be more beneficial to the patient, and lead to a more lasting improvement.

At the time when the drug is exerting its power most actively the patient often feels weakened and out of sorts, and it is then that the use of tonics in combination with the new treatment, as suggested by Dr. McCall Anderson,‡ is not amiss, and may be employed with advantage. Nitro-

* Each powder representing the sixth part of a sheep's thyroid as supplied by Mr. Allen, and 60 grains of the powder being equivalent to one fresh gland as supplied by Ferris, of Bristol. The latter firm also make the powder up into capsules.

† Prepared by Messrs. Burroughs and Wellcome. See "B. M. J.," April 1 p. 701.

‡ "The Treatment of Myxœdema," "The Practitioner," Jan., 1893.

glycerine, too, has been found by Mr. C. J. B. Johnson to "promptly relieve the headaches which came on when the thyroid was freely given."*

I will now quote from a letter I received from my friend Dr. Murray on the 7th May, in which he gives the latest conclusions as regards treatment at which he has arrived. "The treatment consists of two stages—first, removal of symptoms; second, maintaining improved condition. The first stage can be carried out by injections or by the mouth. If injections are used not more than ♏xv. at a time should be injected, as larger doses are apt to cause irritation. Injections may be repeated two or three times a week. If given by the mouth it is best to start with a daily dose of about ♏x.; if not sufficient give it twice. If there is undue acceleration of the pulse diminish the dose. In the secondary stage it is best to give by the mouth, and give the smallest daily dose which keeps the temperature normal or above 97°. I find my original glycerine extract, with carbolic omitted, made by Brady and Martin, most satisfactory to give by the mouth. ʒiss.=one whole sheep's thyroid."

Writing to me again a few days later (May 14th) with regard to his first case—that which has borne the test of time the longest—he says:—"My first case has now no symptom of myxœdema left, and is as well as she could be, both in mind and body, leading an active life as a working man's wife. She takes regularly ʒi. of the thyroid extract each week in daily ♏x. doses. As it is now more than two years since the treatment was first started I think we can fairly conclude that the improvement may be maintained indefinitely." He also stated, concerning the patient whose photo was reproduced in the "Brit. Med. Journ.," August 27, 1892, that she was kept in the improved condition by a daily dose of ♏v. of the extract, and that the photograph taken a year ago represents the present condition very well, except that some of the hair is now seven inches long.

In conclusion, I will quote a remark of Dr. Murray's with which I feel sure many will agree. "If all cases of myxœdema are put on the treatment as soon as diagnosed the insanity of myxœdema ought to cease to exist, and if cretins are fed on some thyroid preparation from youth up they should develop into more useful members of the community." I think it is the duty of all, who in future have the opportunity, to test the truth of what has been said regarding

* "Brit. Med. Journ.," May 6, 1893, p. 955.

this new and wonderful remedy, one which has rightly been said to be "one of the greatest therapeutic triumphs of the age."*

REFERENCES.

Reproductions from photographs of patients who have undergone the thyroid treatment may be found in the following journals:—"Brit. Med. Journ.," Aug. 27, 1892; Jan. 14, 1893, p. 64; April 8, 1893, pp. 737 and 738. "Glas. Med. Journ.," Sept., 1892. "Clin. Soc. Trans.," Vol. xxv., 1892. "Lancet," May 13, 1893. "Sheffield Med. Journ.," July, 1893, etc.

I have to acknowledge my indebtedness to Drs. Murray, Davies, and Mackenzie for the use of some excellent photographs showing myxœdematous patients before and after treatment by the thyroid, which were shown at the meeting of the Medico-Psych. Assoc. on May 18th, 1893.

"The Function of the Thyroid Gland: A Critical and Historical Review," Victor Horsley, "Brit. Med. Journ.," Jan. 30, 1892, and Virchow's "Festschrift," 1891.

Discussion on Myxœdema at the Edinburgh Medico-Chirurgical Society, Feb. 15 and 16, 1893. See "Edinburgh Medical Journal," May, 1893.

Discussion on the Treatment of Myxœdema at the Annual Meeting of the Brit. Med. Association at Nottingham, July, 1892. See "Brit. Med. Journ.," Aug. 27, 1892.

"The Treatment of Myxœdema and Cretinism," Dr. Geo. Murray, "Lancet," May 13, 1893.

"Myxœdema and the Recent Advances in its Treatment," Dr. Hector Mackenzie, "Lancet," Jan. 21, 1893.

"The Treatment of Myxœdema by Thyroid Feeding: Its Advantages and Risks," Prof. Grainger Stewart, "The Practitioner," July, 1893.

"Myxœdema and the Thyroid Gland," being a short account of the supposed uses and functions of the gland, Dr. Lorrain Smith, "The Medical Magazine," Aug., 1893.

"Cases of Myxœdema and Acromegalia Treated with Benefit by Sheep's Thyroids: Recent Observations Respecting the Pathology of the Cachexias following Disease of the Thyroid: Clinical Relationships of Graves' Disease and Acromegalia," Dr. James T. Putnam, "American Journ. Med. Sc.," Aug., 1893.

APPENDIX.

TABLE I*a*.—Cases of Myxœdema Treated by the Subcutaneous Injection of Thyroid Extract.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
1*	Dr. George Murray, of Newcastle.	Brit. Med. Journ., Oct. 10, 1891.	F.	46	4 to 5 years.	3 months: April 13—July 13.	At first ♏xxv. twice a week, afterwards less frequently. Three weeks' interval between last two injections.	Improved with disappearance of most symptoms.	
		Brit. Med. Journ., Aug. 27, 1892.				13 months: April 13, 1891—June 4, 1892.	Same as above. ♏xxv. once a fortnight since July, 189 .	Improvement, but symptoms returned when no injection given for five weeks, and again when the injections were discontinued.	Abscess only after 13 months of treatment.
		See Present Paper.				Over 2 years.			
2*	Ditto.	Brit. Med. Journ., Aug. 27, 189?.	F.	52	12 years.	8 months: Nov. 1, 1891 — July, 1892.	♏xxv. once a week for 4 months, then once a fortnight for 2 months, then once a week again last 2 months.	Improvement (photograph) shows remarkable change in appearance.	Occasional malaise after injection. Once there was loss of consciousness and tonic spasm for a few minutes; at another flushing, nausea and lumbar pain. Once an indurated swelling formed.
		See Present Paper.				Nearly 2 years.		Remains well.	
	Ditto.	Ditto.	F.	62	6 to 7 years.	?	♏xxv. weekly.	"Very marked improvement."	Died from cardiac failure following bronchitis.
4	Ditto.	Ditto.	F.	64	5 years.	3 months.	♏xii. to ♏xxv. weekly.	"Considerable improvement took place," with scarcely any signs left.	Died from cardiac failure.
5	Ditto.	Lancet, Oct. 22, 1892.	M.	44	3 years.	6 weeks.	ʒiii.=2 whole thyroid glands during that time, in 13 injections.	"All the symptoms had practically disappeared." "At the end of August the improvement was so great that no one seeing him could tell that he had had myxœdema."	Local inflammation after fifth injection, with erythematous rash, followed by an abscess.

		Lancet, May 13, 1893.					Glycerine extract by mouth. Since Nov., 1892, has taken regularly ʒi. each week by mouth in daily doses of ♏x. for 5 months.	Kept in good health.	
						January, 1893.		"Quite cured."	
						May, 1893 (8 months).		"At present time in same excellent state of health."	
6*	Dr. Wallace Beatty, of Dublin.	Brit. Med. Journ., March 12, 1892.	F.	45	7 years.	2 months: Dec. 11, 1891 — Feb. 13, 1892.	♏xxv. at intervals of 4 to 10 days, combined with massage.	"Now she is practically cured."	
		Dublin Journ. Med. Sc., May, 1893.				May—Aug., 1892.	A few subcutaneous injections at long intervals, as myxœdema showed signs of returning.	Injections were followed immediately by disappearance of the symptoms, and in October, 1892, "she was quite free from the symptoms of myxœdema," but malignant disease was discovered.	Injections once followed by epileptiform attack, thrice by agonizing pain in lumbar region, and once general œdema of face and feeling of weakness. Died (Feb. 28, 1893) from malignant disease of omentum.
7*	Ditto.	Dublin Journ. Med. Sc., May, 1893. Lancet, May 27, 1893.	F.	50	6 years.	1 month: March 4, 1892—April 2, 1892.	Nine injections given during the month, extract of 2 glands in all (♏120).	"The improvement was very marked and rapid." No symptoms of myxœdema left.	Pain in head and aching in limbs. Twice the injections were followed by suppuration, the last by phlegmonous erysipelas of the arm.
8	Dr. Ernest Carter, of County Asylum, Wittingham, Lancashire.	Brit. Med. Journ., April 16, 1892.	F.	43	1 year.	3½ months: Oct. 21, 1891—Feb. 7, 1892.	♏xxv. twice a week.	"Improvement in bodily and mental condition," especially the former.	Febrile attack with slight rigor, and formation of an abscess.
9*	Dr. Arthur Davies, of London.	Brit. Med. Journ., April 30, 1892. (Shown at Clinical Soc., April 22, 1892.)	M.	43	12 years.	4 months: Dec., 1891—April 30, 1892.	Hypodermic injections, ♏xxv., twice a week.	"Improvement was most marked."	Nil.
		Brit. Med. Journ., Aug. 27, 1892.				7 months: July, 26, 1892.	The same, but with 5 weeks' intermission.	Great improvement. "Regained both mental and bodily activity."	
		Letter, Aug. 10, 1893.				18 months: Aug. 10, 1893.		Maintained by occasional doses.	

TABLE I*a* (*Continued*).—Cases of Myxœdema Treated by the Subcutaneous Injection of Thyroid Extract.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill Effects.
10*	Dr. Arthur Davies, of London.	Brit. Med. Journ., Aug. 27, 1892.	F.	43	8 years.		Injections for 6 weeks. After an interval of 2 months was put on thyroid tabloids.	Improved at first, and after a relapse when no treatment again improved.	Nil.
		Letter, Aug. 10, 1893.				16 months.			
11*	Ditto.	Letter, Aug. 10, 1893.	F.	46	7 years.	12 months (Aug., 1893).	Injections for 3 months, interval of 5 weeks, then put on tabloids.	Greatly improved after 3 months, and again after taking tabloids.	Nil.
12	Dr. Claye Shaw, of Banstead Asylum.	Brit. Med. Journ , Aug. 27, 1892.	F.	33	4 years.	3 months: April 9—June 1, 1892.	Injection about every other day; amount not stated.	"Discharged; quite well in all respects."	Twice abscesses formed; at another pain and swelling.
13	Dr. Hearn, of Dublin.	Brit. Med. Journ., Aug. 27, 1892.	F.	?	?	?	?	"Marked beneficial results."	Lividity of skin, tremors, unconsciousness for ¼ hour.
14	Mr. Hurry Fenwick, of London.	Brit. Med. Journ., Sept. 10, 1892. Brit. Med. Journ. and Lancet, Oct. 22, 1892. (Shown at Patho. Society, Oct. 18, 1892.)	F.	?			Very few injection spread over a long period.	Improvement.	No abscesses or elevation of temperature.
15	Ditto.	Ditto.	F.	?			Ditto.	Ditto.	Ditto.
16	Dr. Hadden, of London.	Brit. Med. Journ., Oct. 22, 1892.	?	?			?	Improved.	
17	Ditto.	Ditto.	?	?			?	Ditto.	
18	MM. Bouchard and Charrin, of Paris.	Lancet, Oct. 1, 1892. B. M. J. and Lancet, Oct. 22, 1892. B. M. J. (Epitome), Nov. 12, 1892.	F.	25		3 months.	?	"Practically cured." "Highly favourable, both bodily and mentally."	Intense headache and pains in limbs and chest after injections, and treatment had to be stopped at times.
19	Ditto.	Ditto.	F.	"Older" than last case.		?	?	Ditto.	Ditto.

20	Dr. Alex. Napier, of Glasgow.	Glas. Med. Journ., Sept., 1892. B. M. J. (Epitome), Dec. 3, 1892. Lancet, Oct. 22, 1892. (Shown at Med. Chir. Society, Glasgow, Oct., 1892.)	F.	54	5 years.	2 months: May 12, 1892—July 10, 1892.	ɱxv. every 2 or 3 days as a rule. Sixteen injections given in all.	Much improved, as seen in photograph. "Remarkable improvement, which is maintained now, three months after cessation of treatment."	An abscess once formed.
21	Mr. Cecil F. Beadles, of Colney Hatch Asylum.	Brit. Med. Journ., Dec. 24, 1892. Present Paper.	F.	50	8 years.	3 months: May 10, 1892—Aug. 24, 1892. 15 months, Aug. 5, 1893.	ɱxx three times a week for last two months. Seventeen injections in all. Thyroid powders internally for six months.	Marked improvement both in mental and bodily condition. Improved condition maintained.	Slight nausea occasionally; attack of rheumatic fever; at another time swelling and pain in shoulder.
22	Ditto.	Ditto.	F.	51	"early."	5 weeks: Aug. 24—Oct. 4, 1892.	Fourteen injections of ɱxx. each, usually every other day.	Slight improvement bodily.	
23*	Dr. A. Barron, of Liverpool.	Brit. Med. Journ., Dec. 24, 1892. Liverpool Med. Journ., Jan., 1893. (Referred to by Dr. Pagan Lowe at Bath and Bristol Branch B.M.A., Nov. 30, 1892. Brit. Med. Journ., Dec. 10, 1892.) See Present Paper.	F.	64	8 years.	4 months: May, 1892—Sept., 1892.	ɱxv. twice a week; 30 injections in all; since Sept. had one weekly injection. Now having tabloids.	"Considers herself to be perfectly well." "Returned to her normal condition."-	Nil.
24	Ditto.	Ditto.	F.	55	?	7 weeks, Sept., 1892.	13 injections of ɱxv.	Improvement most marked.	
25	Prof. Mendel, of Berlin.	Brit. Med. Journ. (Epitome), Dec 24, 1892. Lancet, Dec. 10, 1892. B. M. J., Feb. 4, 1893. Deut. Med. Wochensch., Jan. 12, 1893.	F.	58	4 years.	?	Daily injections.	"Much better" physically and mentally, although could still be recognized as myxœdema.	

TABLE Ia (*Continued*).—Cases of Myxœdema Treated by the Subcutaneous Injection of Thyroid Extract.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
26	Dr. W. Hunter, of Nottingham.	Brit. Med. Journ., Dec. 31, 1892 (Nottingham Medi.-Chi. Soc., Dec. 14, 1892). Lancet, Dec. 24, 1892.	?					Adopted with complete success.	
27	Dr. G. E. Hale, of St. George's Hospital.	Brit. Med. Journ., Dec. 31, 1882.	F.	48	15 years.	5 months: Jan. 9, 1892—June 1, 1892.	♏xxv. weekly.	"Great improvement."	No unpleasant symptoms except slight faintness.
28	Ditto.	Ditto.	F.	46	2 years.	3 months: April 5—July 20.	♏xxv. weekly.	Ditto.	Giddiness and headache; weakness in arms.
29	Ditto.	Ditto.	F.	54	7 years.	5 months: March 16—Aug. 16.	♏xxv. weekly, later one every three weeks.	"Marked improvement."	Fainting and nausea, weakness in arms, fainting fits, pain and swelling; abscess.
30	Ditto.	Ditto.		27	1½ years.	3 months: March —June 4.	♏xxv. weekly.	"Slight improvement."	
31	Dr. Chopinet, of Paris.	Soc. de Biol., iv., 1892.	F.	23	2 years.	?	Half a gland in 3 injections fortnightly.	Immensely improved.	Pain in back and general fatigue for 24 hours after injections.
32	Dr. J. Corkhill, of Birkdale.	Brit. Med. Journ., Jan. 7, 1893.	F.	32	5 months, sudden onset and enlarged thyroid.	2 months: Sept. 24 — Nov. 18, 1892.	♏xv. three times a week.	"Recovery." "She looked healthy."	No bad results.
33	Wichmann, of Berlin.	Brit. Med. Journ., Feb. 4, 1893. Deut. Med. Wochensch., Jan. 12, 1893.	F.	35	2 years.	1 month: Aug. 16, 1892 — Sept. 17, 1892.	Nine injections of thyroid extract.	"After 4 injections there was considerable improvement. At last-named date the disease could not be recognized."	
4	Dr. A. James, of Edinburgh.	Brit. Med. Journ., Feb. 18, 1893. (Edin., Stirling, etc., Br. B. M. A., Feb. 3, 1893).	M.	50	?	6 or 8 weeks.	Injection of thyroid juice.	"Greatly improved."	

35	Dr. J. P. Henry, of Lewisham.	Brit. Med. Journ., April 8, 1893.	F.	44	14 years.	5 months—May 14—Oct.	Bi-weekly injections of mxxx. from May 14 to Aug. From Aug. to Oct. had 2 injections in every fortnight. Since fed with raw thyroids.	Vastly improved; œdema greatly disappeared, and face looks natural and at least 10 years younger. Followed by less marked results.	After first injection had an epileptic fit. After 14th injection a small abscess formed. During 19th injection had faintness, with great flushing of upper part of body, and pains in back.
36	Dr. R. H. B. Nicholson, of Hull.	Brit. Med. Journ., April 8, 1893. (East York and North Lincoln Branch B.M.A., March 24.)	F.	25			Injection of ½ a lobe twice a week.	"Great benefit."	
37*	Dr. J. L. Owen (Dr. Hunt), of Sheffield.	Brit. Med. Journ., April 15, 1893. Lancet, April 15, 1893. (Shef. Med. Chir. Soc. March 23). Shef. Med. Journ., July, 1893.	F.	46	2 years.	6 months: Sept., 1892—Mar., 1893. 11 months.	Injection of extract and feeding with raw thyroid glands. Now (Aug.) taking one lobe of the gland once a week.	Marked improvement. "The patient has been relieved of all symptoms."	On 2 occasions alarming symptoms of œdema of face occurred during the injection.
38*	Dr. Little, of Dublin.	Lancet, May 27, 1893. (Royal Academy of Medicine in Ireland, April 17, 1893.	F.	30	4 years.	8 months.	At first hypodermic injections for two months, and subsequently by mouth Juice of one thyroid in week when used hypodermically and two when eaten.	"Most satisfactory."	Nil
39	Dr. J. K. Barton, of Mentone.	Dublin Journ. Med. Sc., May, 1893.	F.	58	3 years.	2 months: Jan. 26—March 30, 1893.	First month had injections every other day (mxv.), then every third day.	"Felt much better."	Transitory feeling of faintness, nausea, or burning.
40*	Dr. W. Dobbin, of Banbridge, Ireland.	Brit. Med. Journ., Feb. 4, 1893. See Present Paper.	F.	40	4—5 years.	13 months.	For six months hypodermic injections twice a week. Afterwards thyroid juice or tabloids internally twice a week.	"Considers herself well."	An abscess once.

TABLE I*b*.—Cases of Myxœdema Treated by the Ingestion of Thyroid Preparations.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
41*	Dr. Hector Mackenzie, Royal Free Hospital, London.	Brit. Med. Journ., Oct. 29, 1892. Lancet, Oct. 15, 1892. Lancet, Oct. 29, 1892.	F.	40	4 years.	1 month: July 27, 1892—Aug. 17, 1892.	16 thyroid glands given by mouth at irregular intervals twice at a meal; and in addition once two drachms of extract given by mouth.	"A very marked change for the better." "The existence of the disease would probably not suggest itself to anyone seeing her now for the first time."	Nausea, vomiting, and aching pains at first administration; vomiting on five occasions.
						Aug.—Oct.	One thyroid twice a week.	Oct. 29, 1892: "Looks and feels very well." Jan., 1893: "Cured of Myxœdema." "After a fortnight she had markedly improved, and had now for six months been practically well."	
		Lancet, Jan. 21, 1893. Brit. Med. Journ. and Lancet, Mar. 4, 1893. (Shown at Chir. Soc., Feb. 24.) See present paper.				12 months: Aug. 5, 1893.	Expressed juice of a whole thyroid gland once a week, or three White's powders a week.	"In very good health, with no sign of myxœdema whatever."	
42	Dr. E. L. Fox, of Plymouth.	Brit. Med. Journ., Oct. 29, 1892.	F	49	?	4 months: June 2, 1892—Sept. 22, 1892.	At first a glycerine extract of the gland, made from half a thyroid a day twice a week; afterwards half thyroid minced and fried twice a week, with the extract once a week.	"She considered herself well."	Became extremely weak for a time.
		Lancet, Dec. 3, 1892. (Shown at Plymouth Med. Soc., Nov. 9, 1892).				Nov. 9, 1892.	Extract once a fortnight.	Remains in improved condition.	

43*	Dr. H. Handford, of Nottingham.	Brit. Med. Journ., Dec. 31, 1892. (Nottingham Med. Chir. Soc., Dec. 14, 1892.) Letter, Aug. 10, '93.	F.	56	5 years.	10 months: Oct., 1892—Aug. 10 1893.	Fresh glycerine extract prepared in the hospital, ½ a thyroid every other morning for the first week, afterwards twice a week. Since first 9 weeks has taken a tabloid twice weekly.	"Great improvement, so much that patient is not very willing to continue treatment—considering herself well."	None except a little depression while taking the extract every other day.
44	Dr. T. McCall Anderson, of Glasgow.	Practitioner, Jan., 1893 (Vol. 2, No. 1).	F.	30	10 years	onths.	Extract given by mouth, in addition to arsenic and iron internally.	"The mental and bodily habitude has entirely disappeared, and the speech and intellectual faculties are perfect." Photo.	
45	Dr. E. Cresswell Barber, of Brighton.	Brit. Med. Journ., Jan. 7, 1893.	M.	53	7 years.	1 month: Nov. 12, 1892—Dec. 3, 1893.	One thyroid gland at a time—5 in all.	"Quite a changed appearance." Due to loss of myxœdematous characteristics.	Headache and pains in back and limbs; nausea, weakness, vertigo, and palpitation on stooping.
46	Dr. Robert A. Lundie, of Edinburgh.	Brit. Med. Journ., Jan. 14, 1893.	F.	54	14 years.	After 6 weeks' injections, Oct., 1891.	Injections in larger doses than Murray's.	Improvement rapid and satisfactory (then stopped, and after 5 weeks patient relapsed.)	Pains and abscesses after injections; once a severe attack of heart failure.
						6 months: July, 1892—Dec., 1892.	Extract by mouth representing 1-6th part of sheep's thyroid twice weekly.	"No one would suspect that she had suffered from severe myxœdema.' Photo.	No bad symptoms.
		B.M.J. & Lancet, Feb. 25, 1893. Edin. Med. Journ., May, 1893.				18 months, with intermissions.	1-18th oz. of sheep's thyroid daily.	Kept in good health.	
47	Dr. C. Holman, of London.	Brit. Med. Journ., Jan. 21, 1893.	F.	44	Over 7 years.	3 months: Oct. 12, 1892—Jan. 21, 1893.	One whole gland (2 lobes) every other day. After first fortnight ½ 1 be every other day. Later took ½ a lobe once a fortnight.	In 9 days "all symptoms better." Now "there is nothing to be seen to indicate that she has ever had myxœdema."	Tumultuous action of heart and sleeplessness, and slight faintness.
48	Dr. Arthur Davies, of London.	Lancet and Brit. Med. Journ., Feb. 4, 1893. (Clinical Society, Jan. 27, 1893.) Letter, Aug. 10, '93.	F.	47	6 years.	7 months.	Thyroid extract in powder—1-8th of entire thyroid of sheep every day in tepid beef tea.	"All had greatly benefited under treatment." "Rapidly improved."	Nil.

TABLE Ib (*Continued*).—Cases of Myxœdema Treated by the Ingestion of Thyroid Preparations.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
49*	Dr. Arthur Davies.	Lancet and Brit. Med. Journ., Feb. 4, 1893. (Clinical Society, Jan. 27, 1893.)	F.	59	10 years.	7 months.	Three months' treatment by thyroid tabloids	"No trace of myxœdema."	Nil.
50*	Ditto.	Letter, Aug. 10, '93. Ditto. See present paper. Lancet and B.M.J., Feb. 4, 1893.	M.	45	6 years.	7 months.	Thyroid extract in powder—1-8th of entire thyroid of sheep every day in tepid beef tea.	"All trace of myxœdema was gone in 3 months,"	Nil.
51*	Ditto.	(Clinical Society, Jan. 27, 1893.)	F.	54	4 years.	4 months.	Thyroid tabloids.	Improved markedly.	Nil.
52	Dr. Pasteur, of London.	Ditto.	F.	55	17 years.		Raw gland twice a week, at first ½ a gland, and later a whole one daily.	"Much benefited." "Markedly improved."	Toxic symptoms developed after 5 glands with feebleness of heart, so dose reduced.
53	Dr. Calvert, of London.	B.M.J., Feb. 4, 1893; also B.M.J. April 15, 1893.	F.	?	12 years.		Fried thyroid gland. ½ a thyroid three times a week.	"Vastly benefited." "Getting better rapidly."	
54	Prof. Howitz, of Copenhagen.	Semaine Méd., Feb. 8, 1893. Deut. Med. Woch., March 16, 1893.	F.	42		March 22, 1892—July 6, 1892. Over 3 months.	Feeding with thyroid of calves; 4 lobes of lightly cooked calves' thyroid daily.	"The result was excellent." Great improvement in the course of 3 weeks. Several relapses "have all been quickly cured by the same treatment."	Slight steno-cardiac attacks, which necessitated its temporary suspension.
55	Dr. Byrom Bramwell, of Edinburgh.	Brit. Med. Journ. and Lancet, Feb. 25, 1893. (Edin Med. Chir. Soc., Feb. 16, 1893.) Edin. Med. Journ., May, 1893.	F.	?	5 years.	3 months: Nov. 8, 1892 — Feb., 1893.	½ sheep's thyroid internally on alternate days, afterwards reduced in amount; given raw chopped, and put in wafer-paper.	"In four days a great change for the better began to take place." "Now practically cured." Sufficiently well to be a housekeeper	Derangement of gastro-intestinal system; pains and tendency to faint.
56	Ditto.	Edin. Med. Journ., May, 1893.	F.	33	3 years.	2 months: Dec. 26, 1892 — Feb., 1893.	First with 1-8th of thyroid (¼ lobe) daily, afterwards with ¼ and later with ½ thyroid daily. Chopped and in rice-paper.	"Resuming her normal condition." Looked "15 years younger."	Pains, palpitation, and debility.

57	Dr. A. Bruce and Prof. Fraser, of Edinburgh.	Ditto.	F.	?	?		30 grs. of thyroid extract twice weekly during the first month.	Greatly improved within a week.	Headache and occasionally pains in limbs.
58	Dr. Foulis, of Edinburgh.	Ditto.	?	?	?		?	"Had done very well."	
59	Ditto.	Ditto.	?	?	Advanced.		Single dose of ¼ of a sheep's thyroid.		Died within 24 hours from exhaustion and diarrhœa.
60	Dr. John Thomson, of Edinburgh.	Edin. Med. Journ., May, 1893. (Edin. Med. Chir. Soc., Feby 16, 1893.)	F.	51	Over 10 years.	1 month, Dec. 22, 1892.	¼ of sheep's thyroid by mouth twice a week.	"No change."	Slight headache after third dose.
						Dec. 31.	½ thyroid twice a week.		On one occasion had severe angina-like pains, on another fainted.
						Jan. 17, 1893.		"Swelling almost entirely gone."	
						Jan. 27.			Died from cardiac failure.
61	Dr. G. H. Melville Dunlop, of Edinburgh.	Ditto.	F.	46	5 years.	4 months, Oct. 8, 1892.	♏xx of thyroid extract by mouth three times a week.	Improvement noted in 10 days.	Aching pains in limbs, neck, and chest. Irregular action of heart.
						Nov. 20.	Dose reduced to ♏xx. twice weekly.		
						Dec. 2.	Reduced to ♏xv. twice a week.	"Says she feels quite well and perfectly cured."	
						Jan. 10, 1893.	Now having ♏xv. once a week.		
						Jan. 18, 1893.	♏xv. once a fortnight.	Feb. 1st, 1893: "Continues quite well."	
62	Ditto	Ditto.	F.	?	12 years.	3½ months, Oct. 18, 1892.	♏xx. of thyroid extract twice weekly.	In a week "the excitement had quite gone," and improvement in body began.	
						Nov. 12.	Dose reduced to ♏xx. twice a week.		Severe aching pains in limbs and chest and neck.
						Jan. 14, 1893.	Now given every alternate week.		
						Feb. 1.		"Many of her friends scarcely recognized her."	

TABLE I*b* (*Continued*).—Cases of Myxœdema Treated by the Ingestion of Thyroid Preparations.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
63	Dr. G. H. Melville Dunlop, of Edinburgh.	Edin. Med. Journ., May, 1893. (Edin. Med. and Chir. Soc., Feb. 16, 1893.)	F.	43	3 years.	3 months, Nov. 18, 1892 — Feb. 14, 1893.	At first ♏xx. of extract administered thrice weekly, afterwards dose reduced to ♏xx. twice a week, then to ♏xx. once a week.	Improvement noticed after a week. "Mind is much clearer." "All the symptoms yielded to treatment in a couple of months."	
64	Ditto.	Ditto.	F.	56	9 years.	1½ months: Dec. 31, 1892 — Feb. 12, 1893.	♏xx. of thyroid extract thrice weekly.	Change for better noticed in a week. Improvement so marked that a friend "failed to recognize her."	Weakness.
65	Ditto.	Ditto.	F.	48	20 years.	1 month: Jan. 21, 1893 — Feb. 14, 1893.	♏xx. of extract twice weekly.	"Marked difference," and "her spirits are markedly improved."	Nausea and loss of appetite; aching pains.
66	Ditto.	Ditto.	M.	63	18 years.	Jan. 26—Feb. 11, 1893.	1-6th of a thyroid gland administered twice a week.	Slight improvement noted in 10 days' time.	Nausea and restlessness.
67	Dr. H. M. Church, of Edinburgh.	Ditto.	F.	60	"6 months."	?	Thyroid gland.	"Improved very much."	Severe prostration for 48 hours following an overdose. Swelling of parotid and submamillary glands.
68	Dr. Stalker, of Dundee.	Ditto.	?				?	"With success."	
69	Ditto.	Ditto.	?					Ditto.	
70*	Dr. Watson Williams, of Bristol.	Brit. Med. Jour. Feb. 18, 1893. (Bath and Bristol Br. B.M.A., Jan. 25, 1893.) Private Letter, Aug. 16, 1893.	F.	48	13 months.	10 months Oct. 22, 1892 — Aug. 10, 1893.	22 thyroids in sandwiches in two weeks. After an interval of one month, extract given = ½ lobe twice a week. Recently pills (¼ lobe) three times a week.	"Immense improvement. Perfectly free from all unhealthy symptoms." "Can walk five miles without difficulty."	Great cardiac enfeeblement and weak pulse from excessive dose, which recovered with use of cardiac tonics.

71	Dr. Grainger Stewart, of Edinburgh.	Edin. Med. Journ., May, 1893. The Practitioner, July, 1893.	F.	38	9 years.	2 months: Feb. 15—April 24.	30 grs. of uncooked sheep's thyroid every third day in wafer-paper; afterwards increased to 50 grs., and then to one drachm.	"Most satisfactory." "She describes herself as feeling in all respects infinitely better."	Various discomforts felt as oppression in chest, itching and burning sensations, weakness and soreness. In addition had four serious attacks of heart failure with severe dyspnœa.
72	Dr. Menzies (referred to by Dr. Bramwell).	Edin. Med. Journ., May, 1893.	?				Thyroid feeding.		
73	Dr. Hadden, of London.	Brit. Med. Journ., March 4, 1893. Lancet, ditto. (Clinical Soc., Feb. 24.)	F.	40		1 month	Powdered thyroid extract (thyroid gland powders).	"Improved remarkably." "She improved very rapidly, and in about a month she was practically well."	
74*	Dr. Robert Kirk, of Glasgow.	Lancet, March 11, 1893.	F.	42	6 years.	3 months	Fresh gland daily (3 to 10 gr.) by the mouth of Burroughs and Wellcome's extract, or an home-made extract of B. and W.'s tabloids.	"Improved in a few days, almost cured in two months, after which small doses given to maintain the result."	Nil.
75*	Ditto.	Ditto.	F.	72	26 years.	4 months	Ditto.	Ditto.	Nil.
76	Dr. E. Carmichael, of Edinburgh.	Lancet, March 18, 1893.	?				Extract and feeding.	Marked beneficial result.	
77	Ditto.	Ditto.	?				Ditto.	Ditto.	
78	Mr. B. J. D. Shapland, of Exmouth.	Brit. Med. Journ., April 8, 1893.	F.	52	10 years.	2 months: Nov. 12, 1892 — Jan. 12, 1893.	Feeding with thyroid gland of sheep; ½ an underdone thyroid gland the first thing every morning with her food up to Jan. 12.	A week later said she "felt better than she had done for years." After 10 days size of face much diminished and hearing improved. Feb. 5: "Feels quite well."	During the last week some feeling of discomfort about neck and shoulders.
79	Dr. Laache.	Brit. Med. Journ. (Epitome), April 15, 1893. Deut. Med. Woch., March 16, 1893.	M.	49		3 months.	Feeding with glycerine extract, or after cooked, with salt and bouillon added. Later the fresh glands finely minced, first of sheep and then of calf.	Discharged well at end of 3 months.	Some unfavourable symptoms appeared with large doses.

TABLE Ib (*Continued*).—Cases of Myxœdema Treated by the Ingestion of Thyroid Preparations.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
80	Mr. R. H. B. Nicholson, of Hull.	Brit. Med. Journ., April 8, 1893. (East York and North Lincoln Br. B.M.A., March 24, 1893.	F.	56	16 years.	8 weeks.	1 lobe of sheep's thyroid for 3 days running, then 1 lobe every week minced or in an infusion.	At end of 8 weeks seemed quite well.	No ill-effects.
81	Dr. H. W. Pigeon, of Hull.	Ditto.	F.	64	3 years.	8 weeks	½ raw minced thyroid lobe was given for 7 days. After 14 days rest ½ lobe given once or twice a week according to pulse rate.	Marked effect on the œdema. "At end of 8 weeks the patient was well."	But caused great muscular and cardiac weakness.
82	Dr. J. H. Benson, of Dublin.	Brit. Med. Journ., April 15, 1893. Lancet, May 27, 1893. (R. Academy of Medicine in Ireland, April 17, 1893.) Dublin Journ. Med. Sc., May, 1893.	F.	50	8 years.	3 months: Jan. 17, 1893—April 17, 1893.	♏x. of thyroid extract, 2 doses daily between meals. Increased to ♏xv. twice daily. Recently a single daily dose of ♏viii. in water.	First 3 weeks without apparent effect. Followed by marked improvement, and now quite changed.	
83	Dr. Cocking, of Sheffield.	Brit. Med. Journ., April 15, 1893. Lancet, ditto. (Shef. Med. Chir. Soc., March 23.) Shef. Med. Journ., July, 1893.	F.	68	Well marked.	2 months.	Thyroid extract by mouth.	Very considerably improved.	
84*	Mr. J. F. Woods, of Hoxton House Asylum, London.	Brit. Med. Journ., May 6, 1893. (Shown at Hunterian Soc., April 12, 1893.) See present paper.	F.	32	15 months.	4½ months: Jan. 20, 1893—June 8, 1893. 6 months: Aug 3, 1893.	At first hypodermic injections of extract twice a week; afterwards powders by the mouth (1-6th of gland). More recently a "thyroid mixture."	"Began to improve on the third day." "Lost most of physical signs of myxœdema, and mentally bright and talkative."	

85*	Dr. Hingston Fox, of London.	Ditto.	F.	42	1-2 years.	April 12, 1893.	Crude sheep's thyroid glands, one weekly. ½ eaten at two days' interval. 11 glands in all.	"Apparently cured." "Mentally the change is also great."	Nil.
86	Dr. F. J. Smith, of London.	Ditto.	F.	59	3 years.		Cooked thyroid glands.	"Much improved."	After a meal of 10 thyroids (taken accidentally) there was nausea, rapid pulse and acute dermatitis of hands, with subsequent peeling of entire skin of hands.
87	Dr. Saundby, of Birmingham.	Brit. Med. Journ., May 6, 1893. (Shown at Birmingham and Mid. Co. Br. of B.M.A., March 24, 1893.)	F.	57		4 months, Nov. 30, 1892.	Administration of thyroid glands. At first feeding with half a lamb's thyroid daily (16 half glands between Nov. 30 and Dec 31)	"No manifest improvement."	
							Brady and Martin's thyroid extract given hypodermically.		Great complaints of pains.
						March 24, 1893.	Thyroid glands, one lobe daily chopped up and made into sandwiches.	"The patient had lost all the characters of myxœdema, and might have been shown as an example of Grave's disease.	
88*	Mr. C. J. B. Johnson, of Birmingham.	Brit. Med. Journ., May 6, 1893. (Shown at Midland Med. Soc., March 22, 1893.)	F.	49	3 years.	7 weeks.	Raw thyroid, commencing with ½ lobe. Now a ¼ of lobe.	"Distinct improvement was discernible on the third day." Now "felt a new woman."	Headaches (relieved by nitro-glycerine).
89*	Dr Lawrie, of Weymouth.	Brit. Med. Journ., May 20, 1893. (Shown at Dorset and West Hants Branch B. M. A., May 10, 1893.)	?				Thyroid gland taken as an article of food.	"Improved wonderfully."	
90	Ditto.	Ditto.	?				Ditto.	Ditto.	
91*	Mr. A. Maude, of Westerham.	Brit. Med. Journ., May 6, 1893. (Shown at South Eastern Branch B. M. A., May 11, 1893.) See present paper.	F.	60	4 years.	2 months: Dec. 10, 1892—Feb. 7, 1893.	Raw sheep's thyroids given pounded once a week for 2 months.	"Mental state much improved. Skin warm and moist."	Fainting; collapsed after taking 2 thyroids. Headache, faintness, and general discomfort.
						8 months: Aug. 5, 1893.	After interval of another two months took tabloids daily for 10 days.		

TABLE Ib (*Continued*).—Cases of Myxœdema Treated by the Ingestion of Thyroid Preparations.

No.	Observer.	Reference.	Sex.	Age.	Duration of Myxœdema.	Length of Treatment when Reported.	Dosage and Method of Administration.	Result.	Ill-Effects.
92*	Mr. F. C. W. Hounsell, of Chudleigh.	Brit. Med. Journ., May 6, 1893. (South Western Branch B. M. A., April 13, 1893.)	F.	65	2 years.	1½ month: June—Aug. 5, 1893.	Half sheep's thyroid twice a week, served on toast at lunch. 10 administrations in all.	"Most satisfactory; all symptoms completely disappeared."	Some trivial aching pains in limbs simulating the pains of influenza, which soon wore off. Some nausea.
93*	Dr. Wilkin Stabb, of Torquay.	Ditto. See present paper.	F.	22	3 years.	7½ months: Dec. 20, 1892—Aug. 5 1893.	Thyroid feeding, at first one lobe twice a week, minced, and with port wine. Now takes powders = 1-3rd gland once a week.	"Striking character." "Seems now to be a healthy person."	Increased lassitude at first.
94	Dr. Hooper May, of London.	Brit. Med. Journ., May 27, 1893. (Shown at Metropolitan Co.'s Br. B. M. A., May 17.)		26		11 weeks.	Thyroid extract and tabloids.	"Remarkable improvement in all her symptoms."	
95	Mr. Cecil F. Beadles (H. G. Shaw), of Colney Hatch Asylum.	Present paper.	F	45	"Early."	6 weeks: Oct.—Sept., 1892.	Raw glands for six weeks on 8 different occasions, at intervals of one or two days.	Slight improvement in mind and body.	Headache and giddiness after early powders; violent pains in abdomen and loss of consciousness after last three.
96	Mr. Cecil F. Beadles (F. Bryan).	Ditto.	M.	33	6 years.	6 months: Feb. 25.	Thyroid powders representing the one-sixth part of sheep's thyroid every other day, then every fourth day.	Great improvement.	Weakness at first. Vomiting with high temp. once.
						Aug., 1893.	More recently 5 grains once or twice a week.		

97	Dr. H. C. Marr, of Woodilee Asylum, Lenzie.	Glas. Med. Journ., Aug., 1893.	F.	51	9 years.	4 months: Feb. 18, 1893—July, 1893.	Quarter of sheep's gland, and after 3 weeks a glycerine extract use (2ozs.=1 whole thyroid) 3i. thrice daily.	"Gradually improved under treatment both mentally and bodily."	Severe headache; muscular pains over body; liability to get excited on 4 occasions.
98	Mr. Edgar Duke, of St. Leonards-on-Sea.	Birmingham Med. Review, Aug., 1893.	F.	42	1½ years.	3 months: Feb., 1893 — June 1, 1893.	Powders representing 1-3rd of gland given every other day, and then daily; 42 in all.	"Mentally active and physically much more so than formerly. There is marked general improvement."	
99	Dr. J. Putnam, of Boston, U.S.A.	American Journ. Med. Sc., Aug., 1893.	F.	48	13 years.	10 months: June 1, 1892—March, 1893.	For first five months tri-weekly injections of a glycerine extract of sheep's thyroid. Then for 2 months thyroids by mouth, 5 or 6 lobes a week. Since Jan. used powders, capsules or pills.	"Slight improvement by an end of one week. In course of six weeks the improvement attracted the attention of everyone. Now she is still anæmic, but as regards any distinct myxœdema she is practically well."	Languor; nausea; thumping in head; dizziness after both injections and feeding. Itching of skin recently.
100	Ditto.	Ditto.	F.	55	2 years.	Feb. 15, 1893— ?	Thyroid powders, 15 grs. every second day, which is equivalent of one lobe of sheep's thyroid.	"Not only the myxœdema, but also the anæmia has for the most part disappeared."	

* See foot note on page 31.

TABLE II.—Cases of Sporadic Cretinism Treated by Means of the Thyroid Gland.

No.	Observer.	Reference.	Sex.	Age.	Treatment Adopted.	Result.
1	Dr. John Lockhart Gibson, of Brisbane.	Brit. Med. Journ., Nov. 12, 1892, and Jan. 14, 1893. (Intercolonial Medical Congress, Australia, Sept. 26, 1892.)	M.	6 yrs.	Grafting of thyroid of lamb in mammary region. July 20, 1891. One year after first operation, grafting of thyroid of lamb intra-peritoneal, May 20, 1892.	Six months after "very marked and steady improvement." Relapsed somewhat. Sept. 4, 1892—"Fairly intelligent looking baby boy." "Cured his myxœdema and lessened his cretinism.
2	Dr. Affleck, of Edinburgh.	Edin. Med. Journ., May, 1893. Brit. Med. Journ., Feb. 25, 1893. (Edin. Med. Chir. Soc., Feb. 16, 1893.)	M.	?	Implantation of thyroid on three occasions, by Mr. Caird.	Greatly improved.
3	Dr. V. Robin, of Lyons.	Brit. Med. Journ. (Epitome), Sept. 10, 1892. Lyon. Med., Aug. 7, 1892.	?	7 yrs.	Injections of fresh thyroid juice daily. Supplemented by grafting.	Improvement was immediate and great. Operation itself successful.
4	Dr. William Robinson, of Darlington.	Brit. Med. Journ., Jan. 7, 1893. Private Letter, August 10, 1893.	F.	10½ yrs.	Weekly hypodermic injections of thyroid extract, beginning with 6 and increasing to 30 minims, for two months. After which one thyroid gland was eaten weekly for several weeks.	"Slightly improved."
5	Dr. John Thompson (for Dr. W. H. Miller), of Edinburgh.	Edin. Med. Journ., May, 1893. Brit. Med. Journ. and Lancet, Feb. 25, 1893. (Edin. Med. Chir. Soc., Feb. 16, 1893.)	F.	4 yrs.	Feeding with thyroids since Dec. 24th, 1892. At first ⅛ and afterwards ¼ of gland twice a week.	"Wonderful success. After 3½ weeks was much better." "Much more intelligent."
6	Ditto	,,	M.	18 yrs.	Quarter of sheep's thyroid twice a week, by mouth. Dec. 25, 1892, to April 12, 1893.	"His appearance has wonderfully improved." Mentally he is distinctly brighter.

7	Dr. E. Carmichael, of Edinburgh.	Lancet, March 18, 1893.	F.	9 yrs.	Hypodermic injections of thyroid extract between April and October. At first ♏x. twice a week, later reduced to ♏x. weekly and then every second week with occasional intervals of four weeks. Feeding with raw thyroids, October to March. Half lobe per week at first, after two weeks 1 lobe per week. Lately 1½ lobes given. Administered in cold beef tea. Total duration of treatment, 11 months.	"After the first few injections the appearance of the child had completely changed. "As week by week passed some mark of improvement was always seen. In Oct. the child began to walk." "Marked improvement in intelligence was seen."
8	Dr. Vermehren, of Copenhagen.	Brit. Med. Journ.(Epitome), April 15, 1893. Deut. Med. Woch., March 16, 1893.	F.	29 yrs.	Administration of thyroidin (powder, obtained by precipitating a glycerine extract with alcohol).	With success.
9	Ditto	,,	?	?	Under similar treatment.	Promises to give a similar result.
10	Dr. Byrom Bramwell, of Edinburgh.	Edin. Med. Journ., May, 1893. (Edin. Med.-Chir. Soc., Feb. 16, 1893.)	F.	8½ yrs.	Thyroid feeding for five weeks.	"The mental condition has become completely transformed." Grown an inch during the five weeks.
11	Mr. A. G. Francis, of Hull.	Brit. Med. Journ., April 8, 1893. (East York and North Lincoln Br. B.M. A., March, 24, 1893.) Private Letter, August 5, 1893.	F.	36 yrs.	Under thyroid treatment.	"Is improving immensely" (Aug., 1893).

Reprinted from the British Medical Journal, Oct., 1893.

THE NATURE OF VACCINE IMMUNITY.*

Presented to the section of Pathology at the Annual Meeting of the British Medical Association held in Newcastle, August, 1893.

By S. P. Kramer, M.D.,

and

Rubert Boyce, M.B., M.R.C.S.,

(From the Pathological Laboratory, University College, London).

The following is a preliminary report of an investigation on the nature of vaccine immunity. The experiments detailed in this account are limited to the calf, but we are engaged in extending them to other animals:

It has been demonstrated by some observers that when immunity to infectious disease has been experimentally produced in animals, the serum of the blood of such animals possesses immunising and even curative properties in the case of the disease in question, when injected into other animals. It therefore seemed very desirable to us to apply this knowledge in the case of vaccinia, a disease which is every day used to confer immunity. Curiously enough, the observations which have been made upon the properties of the blood of vaccinated calves are few, and appear to be limited to French observers. Chauveau injected into the jugular veins of two young horses 500 and 1,000 grammes of blood obtained from a horse in full vaccine eruption. When these animals were subsequently vaccinated typical vaccinia developed. Straus, Chambon, and Menard transfused a calf with 5,500 grammes of blood obtained from a calf seven weeks after vaccination. The calf was inoculated after the lapse of nineteen days, and typical vaccinia was produced.

*The authors desire to express their very great obligations to Dr. Robert Cory for the interest, valuable help, and criticism which he was ever good enough to give them.

Raynaud, operating with quantities of blood varying from 400 grammes to 4 and 6 kilos., obtained mostly negative results; in some cases, however, it is stated that subsequent inoculation failed to cause a reaction.

In the experiments detailed in this report, we have confined ourselves exclusively to the serum, one kilo. of serum representing in weight about 3 kilos. of blood, and we have injected subcutaneously quantities varying from one half to two litres and a-half. The blood in the first five experiments was taken from calves ten or fourteen days after inoculation; in the sixth case, and in cases which are now under observation, the blood has been taken from calves in full eruption.

The blood is received in sterile vessels, under the strictest aseptic precautions. After coagulation the clear serum is drawn off in sterile siphon pipettes; the clearness of the serum and the failure of agar inoculation vouches for its sterility. The serum is daily (in some cases there has been an interval of two or three days) injected subcutaneously in quantities of from 100 c.c. to 300 c.c., and no local reaction of any kind has been observed around the points of inoculation. The calves are vaccinated as soon after the cessation of the serum injection as possible, usually upon the same or upon the following day.

SUMMARY OF EXPERIMENTS.

CALF I:	Weight	136.4 k.
	Serum injected	415 grms.
	Amount of serum pro kilo.	3.04 grms.

Vaccination successful.

CALF II:	Weight	150 k.
	Serum injected	1240 grms.
	Amount of serum pro kilo.	8.27 grms.

Vaccination not successful. This calf was therefore either rendered immune or had a natural immunity.

CALF III:	Weight	125 k.
	Serum injected	1250 grms.
	Amount of serum pro kilo.	10 grms.

Vaccination successful.

CALF IV:	Weight	121 k.
	Serum injected	1310 grms.
	Amount of serum pro kilo.	11.8 grms.
	Vaccination successful.	
CALF V:	Weight	132 k.
	Serum injected	2500 grms.
	Amount of serum pro kilo.	18.94 grms.
	Vaccination successful.	
CALF VI:	Serum injected	1485 grms.
	Vaccination successful.	

The experiments show with one exception that the above large doses of serum failed to produce immunity as regards the inoculation test of cow-pox. The one exception may mean either an artificial or an acquired immunity. Until we have made some further observations upon the calf and the monkey we will not venture to comment upon our results, but, as they stand, they tend to increase our difficulties of holding exclusively to any one theory of immunity.

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AN ANALYSIS OF ONE HUNDRED CASES OF MYCETOMA.

By Assistant-Surgeon **J. E. BOCARRO,**
L. M. & S. Bombay,
Teacher, Hyderabad Medical School.

Much has already been written upon the subject of mycetoma. Carter discovered its parasitic nature; Lewis and Cunningham, in an analysis of several cases, were not convinced of this; recently Kanthack has tried to prove the actinomycetic nature of the parasitic fungus, a view which Carter himself had already become inclined to adopt; and still more recently Boyce and Surveyor have brought forward evidence which shows that there are marked differences between the fungi of the black and white varieties of mycetoma. As, however, further clinical knowledge on the subject is a desideratum, I have collected the following notes from the Hyderabad Civil Hospital registers of the past ten years and, combined with my own notes and experience, now publish them with the view that they may, to some extent at least, help investigation into the etiology and pathology of this disease.

Summary of Analysis of the 100 Cases.

Caste.—In Sind the proportion of Mohammedans to Hindus suffering from this disease is about 86 per cent. of the former to 14 per cent. of the latter. It must be noted, however, that the Mohammedans form the greater bulk of the agricultural population in Sind, and as the disease is prevalent only in rural districts—as is evident from the fact that not one of the patients is reported as being resident in a town—one must naturally expect to find this seeming disproportion between these two main divisions of caste in Sind. As a matter of fact people of all denominations and of every status in life would be equally liable to contract the disease were they exposed to the exciting cause, whatever that may be, under

the same circumstances as those in which the Sindhi Mohammedan ryot exists every day of his life. It would appear, therefore, that the disease is essentially one of the country and not of the town—that is, so far as one can trace the occurrence of the primary lesion—and affects only those whose calling requires them to be out of doors. Cultivators and their wives are hence very liable to this affection.

Sex.—As regards sex, of the total of the 100 cases examined 8 only were females, and of these 6 were Mohammedans, all wives of cultivators, and 2 Hindus, one of whom was the wife of a cultivator, the occupation of the other not being recorded. There was no difference noted in the nature of the tumour in females from that observed in males, and also the history of the cases, where such could be obtained, bore the same analogy to that of the males, especially with reference to causation.

Age.—The limits of age range between twelve and eighty years, and, reckoned in decennial periods, the range between twenty and forty years gives the highest number of cases, as is shown in the figures given below. This point is, perhaps, of importance, as indicating that the cause of the disease is generated from some source or sources beyond the sphere of home life to which the very young and the very old are confined, and this remark, it may be noted, is equally true with reference to sex.

The number of cases of patients suffering from mycetoma at various ages, given in decennial periods, was as follows: Between the ages of ten and twenty, 40; from twenty-one to thirty years of age, 35; from thirty-one to forty years of age, 15; from forty-one to fifty years of age, 7; from fifty-one to sixty years of age, 2; from sixty-one to seventy years, 1; and from seventy-one to eighty years, 1.

Occupation.—As already noted above, both sex and age indicate that the disease is not found in individuals engaged in occupations other than those in the open air. It is also not observed in town residents. The information obtained from the record of the cases confirms this idea. As many as 91 per cent. of

them occurred amongst tillers of the soil and the remaining ones amongst those whose means of livelihood are dependent on work in the open country—*e.g.*, the shepherd and the boatman, or those who are led by force of circumstances at some time or other of their life to travel across rural districts—*e.g.*, the Hindu mendicant and the Mohammedan fakir. Amongst the workers in the open air may also be mentioned the grain and cloth merchants. Dr. Carter states as worthy of note the case of a potter whose right hand was affected and suggests that potters work largely in wet earth with their hands. In one of my cases, that of a potter, the disease had attacked the middle of the sole of the left foot, probably for the same reason.

The part affected.—Hitherto all observers have noticed the disease as having attacked either the foot or hand, or both these extremities at the same time in the same individual, but, as far as I am aware, no cases have as yet been recorded of any part of the trunk being the seat of this affection. The term "Madura foot" applied to the disease is certainly a misnomer, as Dr. Carter states, since the disease is also found to attack the hands, and this remark now becomes doubly significant from the fact of the disease having attacked in two of my cases the region of the right shoulder-blade and the right sacro-iliac joint, the affection in both instances being exceedingly well-marked and leaving no doubt as to the nature of the growth. Both cases were of the black variety. These peculiar situations of the disease are worth noticing with reference to its etiology. Of the 100 cases collected by me, in three only had the malady attacked the hand, the left hand being involved in all three, and in two the leg, of which one occurred in the right and the other in the left leg. The remaining cases, excluding the two quoted above in which the trunk was affected, were foot cases, of which forty-one were cases of the right foot and forty-nine of the left. In three of the foot cases the side affected was not noted. Dr. Carter observes that in his experience the right foot was oftenest affected, and adds that "I know of no *a priori* reason why the right rather than the left foot should be obnoxious to the affection, unless we suppose that it is more liable to accidental injuries,

through which the spores of chionyphe might find unusual facility of entrance into the tissues of the foot." From the cases recorded above it will be seen that, if any such predilection exists, it should be in favour of the left side of the body, for, curiously enough, even the three cases of the disease affecting the upper extremity all belonged to the left hand. The probability, however, is that there is no such distinction to be observed, both sides of the body being equally liable to the affection.

Symptoms.—Generally speaking, the symptoms accompanying this disease are somewhat as follows : In the early stage, when the disease is asserted to have occurred spontaneously—*i.e.*, without any history of such exciting conditions as a pre-existing wound, or abrasion, or sore, or as the result of an accidental injury, or the prick of a thorn—the first symptom noticed is a localised tenderness or uneasiness, followed, in the course of about a fortnight, by a local tumefaction. Subsequently there is an appearance on the spot of a nodular growth, varying in size from that of a pea to that of a small marble, with its deeper attachments diffuse and indistinct. The integument over the part affected is either normal in colour or more often, especially if the tumour has been of long duration, of a blue or purplish hue, and always more or less thickened, indurated and adherent. In course of time this nodule increases, resulting in a more or less pronounced tumefaction. This tumefaction where the foot or hand is concerned may commence on the dorsal, or the plantar, or palmar surfaces, often between the digits and sometimes in the heel. The ball of the thumb or of the great toe, or the pads of areolar tissue and fat along the bases of the fingers and toes, are favourite initial seats of the disease. The deformity resulting is influenced by the site of the underlying tendons and hard tissues. For instance, when the dorsum of the foot is first affected and the diseased mass has travelled to the roots of the toes these digits become flexed and are turned downwards, and if the sole becomes the primary seat of lesion the arch of the foot is invariably lost, the sole, or may be the whole foot, assuming a globose appearance with the toes tilted upwards. Extension of the growth into the interspaces between the digits of the hand or foot causes these digits

to be separated one from another, some being abducted, others adducted, and not unfrequently some are at the same time flexed and others extended. Where the disease begins at the heel and encroaches upon the ankle-joint a misshapen form of talipes equinus is the result. Such information is useful in guiding the knife in the course of the operation of excision and dissection. The primary origin of the disease, so far as I have been able to ascertain from the notes of the cases before me, appears to be referable at the earlier periods to the soft tissues—*i.e.*, the subcutaneous cellular padding or the muscles together with it—and only at a later date do the hard tissues, bones, cartilages, &c., become implicated; in no case, however, has the growth been found to be so superficial as to infiltrate the integument only. It must also be observed that no definite relation as to time could be ascertained between the date of the occurrence of the exciting condition—whether wounds or sores or pricks of thorns, &c., where such exist—and the date of the first appearance of the tumour; the earliest interval recorded in my notes is about fifteen days. Nor could I discover any relation between the size of the tumour—in other words the degree of infiltration—and the time occupied in its growth. Under varying circumstances the growth enlarges, and within a period of between a month and six months it attains a very perceptible size. Sooner or later —perhaps in a year or even in two years, and sometimes more—the tumour begins to gradually soften down here and there, and the pent-up matter evacuates itself through a sinus or several sinuses together, much in the same way as occurs in necrosis and caries or in perineal and ischio-rectal abscesses. The first indication of the appearance of a sinus externally is a nodule varying from a quarter to half an inch in size, and sometimes a bleb or blister, which soon bursts, opens and discharges a thin sero-purulent fluid, occasionally sanious, but always largely mixed with the fine black gunpowder-like bodies of the melanoid variety or the pink roe-like particles of the pale variety of the disease. The detection of these bodies at once establishes the nature of the disease. In advanced stages, extending over periods varying from two to ten or even fifteen years, the general tumefaction becomes more widespread, the

number of sinuses increases and they open out in all directions, numbering sometimes as many as twenty-five or thirty, or more. These sinuses are always more or less tortuous in their course and intersect one another in many places, so that if probes are passed into them their ends can be felt to meet together at some depth in the interior of the tumour; often the cavity of the cyst connected with these sinuses or tunnels may also be detected. The presence of one or more permanently discharging sinuses is not a constant feature with the tumour; sometimes a tumour may be seen which is quite dry externally and the sinus or sinuses are partially or even completely closed up. On the other hand, there may be one or more discharging sinuses without any external evidence of a tumour; such instances are rare. In all cases the part affected, whether hand or foot, or any other region of the body, becomes excessively hypertrophied, and markedly globular. This globose appearance of the tumour is very characteristic, and still more so is the general appearance it assumes at its uttermost development—viz., an enormous globe of hypertrophied tissue drilled all over with holes. Acute pain is never a prominent symptom at any period of the disease, but most patients complain of a slight dull ache, which from time to time at indefinite intervals—four or five times in the course of a year—as far as I can gather from the statements made by those rude and ignorant people, the class of cultivators, tends to become slightly exaggerated. Most of the patients seek admission into the hospital when the disease is well advanced, and then not on account of pain, but because of the discomfort and uneasiness which the tumour causes by its massive size, or owing to its being situated in inconvenient positions, as when affecting the fingers and toes only, or, as in the two cases mentioned above, where the shoulder blade and the sacrum have become the seat of the affection. Another remarkable feature of the disease is the entire absence of any marked constitutional disturbance at any stage of it. The disease is entirely, in fact, a local complaint *ab initio*, and this is seen from the certain and rapid curative results which invariably attend treatment by surgical interference and the equally speedy manner in which the general health of the patient is restored to its normal state after the operation.

Diagnosis.—Sufficient has already been said to show that the finding of the black or pink particles is characteristic. With reference to guinea-worm disease I would here make a passing remark. The idea suggested itself that mycetoma might have some connection with the history of that worm. I may state that so far as Sind is concerned it could hardly be entertained. Guinea-worm disease is not endemic in by far the greater part of Sind and it prevails only in the stagnant pools of the Thar and Parker districts. The few occasional cases seen in the Hyderabad Civil Hospital occurred amongst people who had travelled or been resident in places outside the province of Sind. In a case mistaken for guinea-worm disease, the error in diagnosis occurred because of the uncommon situation and the extent of the mycetomatous growth; it is the only case of its kind on record in this hospital. The disease extended in this case from below the knee to the ankle.

Prognosis.—To expect a spontaneous cure or a cure by remedial measures is beyond my experience; on the other hand, surgical operation, whether undertaken early or late, and regardless of age or sex or even of constitutional debility, gives exceedingly satisfactory results. In fact, it is the only means of permanent cure. provided the surgeon can ensure the successful removal of all traces of the disease in the part operated upon, otherwise the disease is liable to recur, as happened in five of my cases, two of which had been previously operated on unsuccessfully in the dispensaries in Sind. In one case the tumour had been excised by a barber, and two cases were operated upon a second time in this same hospital. All these patients left the Hyderabad Civil Hospital cured. A mortality of about 2 per cent., which has been the result achieved in this hospital, speaks volumes in favour of the chances of recovery. As regards rapidity of recovery it is needless to say that prognosis is far more favourable when the disease is superficial and has attacked the soft parts only than when it is deep and has involved the hard tissues.

Remarks.—Everything points to a definite local infecting agent or agents as the cause of this disease. Local injury, such as the

prick of a thorn, is a common history in the cases which I have examined. The offending thorn in the province of Sind is usually furnished by the Acacia arabica ("babul") or other species of acacia. I have recently had the opportunity of examining inflammatory foci which had formed around "babul" thorns *in situ* in the tissues; but, according to Professor Boyce, who kindly examined the tissues for me microscopically, there were no fungoid elements present. In these cases, therefore, the presence of the thorn merely caused a local irritation.

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THE ETIOLOGY & PREVENTION OF PERITONEAL ADHESIONS AFTER LAPAROTOMY.

BY

M. WALTHARD,

M.D. (M.R.C.S. Eng.),

FIRST ASSISTANT, GYNÆCOLOGICAL CLINIC IN BERNE.

(From the Pathological Laboratory, University College, London.)

THE ETIOLOGY AND PREVENTION OF PERITONEAL ADHESIONS AFTER LAPAROTOMY.

As a rule the formation of peritoneal adhesions after a laparotomy have no disturbing influence on the functions of the abdominal organs, or on the prognosis. I should like, however, to bring forward certain forms of intestinal occlusion which come under the head of strangulation, and to remove which laparotomy is called for, and when not carried out leads to a fatal termination.

In spite of the strict asepsis and the very careful washing out of the peritoneum which is practised at the present day, intra-peritoneal operations are almost constantly followed by adhesions. (1).

I have myself lately had the opportunity of observing, in two patients in which a second laparotomy had to be performed, the existence of adhesions, although the first laparotomy had healed perfectly normally.

Hypothesis and experimental investigation have not failed to endeavour to explain and to prevent the formation of these adhesions. From the Clinical side, the explanations which have been brought forward are, loss of peritoneal

(1) *P. Müller:* Correspondenzblatt f. Schweizer Aerzte, Jahrgang XVI.—*Martin*, *Ohlshausen*, *Gusserow* vide Zeitschrift f. Geburtshülfe u. Gynæcologie, B.D. XV., 1889.—*Fritsche* Centralblatt f. Gynæcologie, 1890, Nr. 29.

surface, the retraction of the stump, the scar, the still position of the intestine, and the contact of the intestine with the operation wound. *A. Martin* has brought forward the above when opiates are administered in laparotomy cases. To hinder the contact of the intestine with the wound caused by the operation, *P. Müller* has recommended the abdominal cavity to be filled with stirilised Sodium Chloride Solution.

Stern (2) endeavoured, supported by experiments, to obtain this result by painting the intra-peritoneal stump with collodium.

The results of these experimental investigations (3) may be divided into two groups:

1st. Those of Kelterborn, who endeavoured to explain the formation of peritoneal adhesions after laparotomy, by the occurrence of infection, in spite of an apparently normal peritoneum.

2nd. Those of Thomson, which, like our clinical experience, showed that adhesions could occur without infection.

That circumscribed peritoneal adhesions may take place from an infective peritonitis will not be contradicted, as these are of sufficiently common occurrence. But an explanation of the adhesion which takes place aseptically between an apparently normal serous surface and the seat of operation, I have not been able to find in the present literature.

I therefore venture to give the results which I have obtained from the experimental side, trusting that they may prove of use as a basis for further experimentation.

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(2) *R. Stern:* Beiträge zur klin. Chirurgie von *Bruns*, *Czerny*, *Krönlein* und *Socin*, Bd. IV., Heft 3.

(3) *Sænger*, Archiv f. Gynæcolog., Bd. XXIV.—*Waldeyer* u. *Spiegelberg*, *Virchow's* Archiv, Bd. XLIV.—*Wagner*, Archiv f. klin. Chirurgie, Bd., XX. — *Dembowski*, Archiv f. klin. Chirurg., Bd. XXXVII.—*Kelterborn*, Centralblatt f. Gynæcologie, 1890, Nr. 51.—*Thomson*, Centralblatt f. Gynæcologie, 1891, Nr. 5.

The animals experimented upon were cats and rabbits. In each case the animal was chloroformed, and fixed on its back, the abdomen being treated in exactly the same manner as a patient would be under aseptic laparotomy, viz., After shaving, washing with soap and brush and warm water; disinfection with acid perchloride, 1 in 1000, rinsing with sterile sodium chloride and carbonate solution (Favel's).

The disinfected hands were washed with the same solution to get rid of the perchloride.

Everything that was to come in contact with the serous membrane, &c., was sterilised beforehand by heating.

In a former series of experiments (4) upon supravaginal amputation of the uterus in the rabbit, I found, in spite of strict aseptic precautions, fibrous adhesions in the lower part of the vesico-uterine pouch, between the normal anterior serous covering of the uterus wall and the normal serous covering of the posterior part of the bladder. Yet these serous surfaces seemed in no way to have been disturbed, either by ligatures or by the hand of the operator. The atmospheric air alone had come in contact with the vesico-uterine region, from the moment of opening the peritoneal cavity, until the replacing of the viscera. This observation directed my attention to finding out whether the atmospheric air had any disadvantageous influence on the normal serous surface, and if it had, whether protecting the serosa during the operation would prevent the formation of adhesions.

I therefore operated on six rabbits after the previously mentioned disinfection. The abdominal cavity was opened and the uterus quickly pulled out and covered with sterile gauze, soaked in Favel's solution. The intestines and other

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(4) Archiv f. experimentelle Pathologie und Pharmakologie, Bd. XXX, p. 279.

organs were similarly protected by gauze. By continued new application of warm soda solution the serous surfaces were constantly kept at a proper temperature and moisture, and only so much of them exposed as was actually necessary for the application of ligatures, &c. On the post-mortem examination of animals so treated, no adhesions were found, and the serous surfaces were smooth and shiny. The harmful influence of the air seemed thus to have been proved.

Still further, however, to show the effect of the air, the same manipulative procedure was carried out in five further experiments on cats; the only difference being that the surfaces were exposed to contact with the air. The autopsies, twelve days after the experiments, revealed adhesions over the exposed surfaces. In no place could I find adhesions between the intestines and abdominal wound. On the other hand, the serous surface of the mesentery seemed not so transparent in this position as beyond the reach of the operation. A control experiment was carried out, in which the exposed organs were shielded from contact with the air by sodium chloride carbonate gauze. The autopsy of this animal showed entirely normal appearances, there being neither any adhesions nor thickening of the serous surfaces.

These experiments seemed clearly to show that the changes in the serosa were due to contact with air.

Already it had been pointed out that long exposure to the air caused changes in the serosa. Wagner (5) in his experiments shewed that by pumping air into the abdominal cavity of rabbits, that after four days the serosa was thickened and covered with flakes, and that fatty degeneration of the epithelium had taken taken place. After eight to ten days he found an excessive granulation of the cicatrix.

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(5) Archiv f. klin. Chirurgie, Bd. XX.

Also Delbet (6) mentions microscopical alterations of the upper endotheial layers, probably of the nature of a necrosis, after long contact with the air.

It was a striking fact that although in my own cases the thickening of the mysentery showed distinctly enough the effects of the air the formation of adhesions was much less marked on the surface of the intestines. No one will doubt that here the peristaltic movements hindered their formation; but in order to investigate this point more minutely, the following three experiments were performed:

A piece of intestine was exposed to the air for twenty minutes, and then folded so that two serous surfaces should be in contact. They were fixed in position by stitches and replaced in the abdominal cavity. The autopsy twelve days later showed marked adhesions at the place of contact between the loops. The serosa, which was not in contact, showed thickening. The same results were obtained after exposure to the air, when opium was given to hinder peristalsis. It would seem, therefore, that the movements of the intestines break any adhesions which may occur.

From the above experiments I think the following conclusions may be drawn:

1. By long contact with the air, the upper layer of cells of the serosa are damaged. Therefore the air is of etiological moment in the production of peritonitis.

2. When two serous surfaces, altered as above, are kept in contact for a certain time, adhesion occurs.

3. If, however, the actual serous surfaces remain in contact for only a short time, there is simply thickening of the serosa.

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(6) Centralblatt f. Chirurgie 1878, S. 522.

Nor, on the other hand, under the same aseptic precautions, does adhesion take place between a normal and an injured serous surface. I have many times convinced myself that those substances (products of bacteria) are not produced on the injured surface, which lead to the alteration and adhesion of the opposed surface.

The question now remains to be considered, how the air, apart from the question of microbes or dust particles, acts injuriously upon the peritoneum.

There are two possible ways of accounting for its harmful action. The air may act chemically. Like in the experiments of Kühne, Scholz, and Pflüger, the hæmoglobin of the slight extravasation which is always present in a wound, in spite of the greatest care, may convert the oxygen of the surrounding air into ozone. Oxygen would be then set free, which in the nascent condition would act as a powerful oxidising agent upon the serous surface.

Secondly, the air may act physically by simply withdrawing water from the serous surface. This could happen where the air of the operating room is not saturated for its temperature.

In order to investigate these points I constructed a small apparatus, consisting of a glass bell jar, furnished at the top with a thermometer; an inlet tube near the mouth of the vessel served to conduct air or steam, or the constituents of the air, into the interior, whilst a tube in the opposite side served as outlet when the bell jar was placed in position over the peritoneal surface. In this way a constant stream of air could be kept up in the interior of the bell jar, of known temperature and of various degrees of saturation.

In the following experiments, after the abdomen was opened, the abdominal organs were slightly withdrawn and the bell jar was placed over them. In order to exclude infection and the action of dust, the air was filtered through wool for the twenty minutes during which the three experiments lasted. At the end of that time the organs were replaced and the abdominal wound closed. Twelve days afterwards the autopsies showed the presence of adhesions.

These results agree completely with those of Thomson, who, operating in a room especially prepared to be as free from germs as possible, came to the conclusion that adhesions could occur aseptically. The adhesions were free from micro-organisms, as shewn by microscopic examination and inoculation.

There remained, therefore, only to decide whether the air acted purely physically, chemically, or physically and chemically.

For this purpose, three experiments were made, in which the air was mixed with steam, the bell jar registering a temperature of 38°C, and the moisture condensing upon the inner surface of the glass. In the three experiments there were no adhesions, precisely as in the case of the saline solution.

Adhesions could therefore be prevented by guarding against drying.

To prove the chemical action of the gas constituents of the air, oxygen, nitrogen, and CO_2 were respectively mixed with steam, and the abdominal organs, in three series of experiments of three each, exposed to their action. In the case of oxygen no adhesions occurred, nor was any nascent oxygen apparently formed, as shewn by the potassium, iodide, and guiacum tests. In the case of the CO_2 and N_2 there were likewise no adhesions.

We may therefore as the result of these experiments, conclude that the air during its long contact with the serous surface, acts harmfully, not only on account of its well known property of carrying infection and irritating particles, but also by drying the surface and causing the death of the most superficial cells. That this death might be produced by the cooling effect of the current of air, and the resulting contraction of the vessels, and diminished nutrition, there is no doubt. But dry air heated to the temperature of the body likewise produced similar results, as I convinced myself in three experiments.

Corresponding with these results, the serosa shewed microscopically, after a few minutes' contact with the air, a perceptible loss of its normal shining appearance.

The harmful effect of the dry air was further shown by the smaller quantity of micro-organisms (1000 times less) necessary to produce infection and a fatal peritonitis. (7)

Bringing together the above facts relating to the ætiology and mode of origin of peritoneal adhesions after laparotomy, I believe that we may state,

That long continued contact with the air causes a drying and necrosis of the upper cell layers of the peritoneum, a process which, in spite of aseptic precautions, is of ætiological significance in the production of adhesions.

Clinical experience supports this statement. The value of rapidity of operation and of exposing the peritoneum for as short a time as possible, is well known. The prognosis in the cases of rapidly conducted laparotomies

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(7) *Walthard*, Experimenteller Beitrag zur Kenntniss der Aetiologie der eitrigen Peritonitis nach Laparotomie (sogen. Operativperitonitis). (Archiv für experimentelle Pathologie und Pharmacologie, 1892.)

in the Bern Clinik is better. Aseptic peritoneal adhesions, or purulent peritonitis (8) from accidental infection, are most liable to occur in those operations, which, like that of enucleation of a tumour from the pelvis, require considerable time and lead to drying of the peritoneum.

I have to thank my honoured Chief, Professor P. Müller, for the opportunity of clinically verifying and controlling my experiments upon animals.

Thus in a series of forty-six laparotomies, (9) where the exposed peritoneum was kept moist by gauze dipped in the soda-salt solution, and where the extravasated blood and cystic fluid was washed out of the abdomen by means of a similar fluid, in no case was there purulent peritonitis, and in no case dry peritonitis with ileus phenomenon. The flatulence disappeared in the severest cases on the first or second day after operation, whilst in the former cases of dry asepsis it lasted to the fourth and fifth days.

I believe that, supported by these experimental researches and forty-six laparatomies, I can confirm and further extend my conclusions regarding peritonitis after operations (10).

I can, namely, state that DRY ASEPSIS is in principle to be avoided, as well as the harmful abdominal toilet, necessitating the drying and wiping of the peritoneal folds by dry material. On the contrary, MOIST ASEPSIS is to be employed in long operations.

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(8) Vide Archiv für exp. Pathologie und Pharmacologie, Bd. XXX.

(9) Es kamen nur Laparotomien in Betracht, bei denen nach Beendigung der Operation die Abdominalhöhle ohne Drainage und ohne Tamponade geschlossen wurde : 14 Ovariotomien, 14 Castrationen, 8 Myomotomien, 3 conservative Kaiserschnitte, 4 Probelaparotomien, 1 Bauchhernie, 1 Extrauteringravidität, 1 acute Peritonitis.

(10) Archiv für exp. Pathologie und Pharmacologie, p. 299.

Under "moist asepsis" I would include the prevention of drying of the serosa, and the swilling out of the abdomen of all extravasated blood and cyst contents; in contradistinction to the wiping out of the abdominal cavity by sponges, or in other words, the rubbing into the serosa, infected material, blood, &c. For washing, Favel's solution at 38°C may be employed as a "normal" fluid. The more regularly and continuously the serosa is moistened, the more physiologically active does it remain; the whole body, as well as the parts at the seat of operation, suffer less from cooling, the serosa is well nourished, and the laparotomy has a smooth course.

Dulling of the peritoneal surface may be taken as the sign of commencing drying.

In conclusion, I offer my best thanks to Professor P. Müller, Professor Horsley, and the British Medical Association, for their assistance.

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